



XI SIMPOSIO INTERNACIONAL AVANCES EN EL TRATAMIENTO DE TUMORES DIGESTIVOS

HOTEL INTERCONTINENTAL PRINCESA SOFÍA. BARCELONA 12 Y 13 DE DICIEMBRE DE 2003

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PONENEN

CIAS



Índice Index

- Cáncer colorrectal: una oportunidad para la investigación**
Eduardo Díaz-Rubio
*Hospital Universitario Clínico San Carlos, Madrid. **España**6*
- Tratamiento quirúrgico de las metástasis hepáticas de Cáncer colorrectal**
Joan Figueras
*Hospital Universitario de Bellvitge, Barcelona. **España**12*
- Primary or secondary surgery of colorectal liver metastases**
René Adam
*Hepatobiliary Centre, Paul Brousse Hospital. **France**14*
- The role of radiofrequency ablation (rfa) in the treatment of liver metastases (lm)**
ELIAS Dominique
*Gustave Roussy Institute, Villejuif. **France**18*
- The Role of Radiation Therapy in the Treatment of Esophageal Cancer**
Bruce Minsky
*Memorial Sloan Kettering Cancer Center, New York. **United States**20*
- Esophageal Cancer: Randomized phase III trial. Chemoradiation with and without surgery**
Michael Stahl
*Kliniken Essen-Mitte, Essen. **Germany**22*
- Treatment of Locoregional Esophageal Cancer**
Susan Urba
*University of Michigan Medical Cancer Center, Ann Arbor. **United States**24*
- Esophageal cancer: The role of PET scan in the clinical decision**
Sigrid Stroobants
*University Hospital Gasthuisberg, Leuven. **Belgium**34*
- Cetuximab in the treatment of colorectal Cancer**
Josep Taberner
*Hospital Vall d'Hebron, Barcelona. **España**38*
- Estado actual de otros anticuerpos anti-EGFR y de los inhibidores de tirosina quinasa de EGFR**
Andrés Cervantes
*Hospital Clínico Universitario, Valencia. **España**40*
- Cox-2 inhibitors in the prevention and treatment of gastrointestinal tumors**
Ernest Hawk
*National Cancer Institute, Bethesda. **United States**44*
- Bases teóricas para un tratamiento selectivo del Cáncer colorrectal**
Eva Martínez-Balibrea
*Hospital Universitari Germans Trias i Pujol, Badalona. **España**48*



The role of molecular markers in the adjuvant treatment of colorectal Cancer
Wei Zhou
Emory University, Atlanta.
United States.....52

Pharmacogenomics in Colorectal Cancer
Heinz Joseph Lenz
Norris Comprehensive Cancer Center, Los Angeles. *United States*.....56

Farmacogenómica y cáncer colorectal
Experiencia del Grupo TTD
José Luis Manzano Mozo
Hospital Universitari Germans Trías i Pujol. *Badalona*.....60

Treatment of advanced colorectal cancer
Irinotecan in combination treatment
Claus-Henning Köhne
Universitätsklinik Carl Gustav Carus, Dresden. *Germany*.....64

Oxaliplatin in combination chemotherapy for advanced colorectal Cancer
Philippe Rougier
Hospital Ambroise Pare, Boulogne-Billancourt. *France*.....68

The role of the combination of oxaliplatin, irinotecan and 5-FU in advanced colorectal Cancer
Eric Van Cutsem
University Hospital Gasthuisberg, Leuven. *Belgium*.....76

¿Capecitabina o infusión continua de 5-FU?
Bartomeu Massutí
Hospital General Universitario, Alicante. *España*.....78

¿Cómo tratar a los pacientes ancianos con Cáncer colorrectal?
Javier Sastre
Hospital Universitario Clínico San Carlos, Madrid. *España*.....86

Cáncer de colon avanzado. Experiencia del Grupo TTD
Enrique Aranda
Hospital Universitario Reina Sofía, Córdoba. *España*.....92

Strategies to optimise chemotherapy in the treatment of advanced Colorectal Cancer
Alberto Sobrero
Medical Oncology Ospedale S. Martino, Genova. *Italy*.....98



Cáncer colorrectal: una oportunidad para la investigación

Eduardo Díaz-Rubio

Hospital Universitario Clínico San Carlos, Madrid. *España*

RESUMEN

El cáncer colorrectal representa un verdadero problema epidemiológico de salud pública dada su elevada incidencia y mortalidad. Concretamente en España y según los datos disponibles del Instituto Carlos III para el año 2000 el número de defunciones anuales es de 6591 para los hombres y de 5380 para las mujeres, lo que representa el 11% y el 15% respectivamente de las muertes por cáncer. En cuanto a la incidencia anualmente se diagnostican 14.202 casos en los hombres y 11.461 en las mujeres. Es preciso decir que mientras los datos de mortalidad se encuentran muy ajustados y bien recogidos (provenientes de los certificados de defunción y por tanto del Instituto Nacional de Estadística), podría no ocurrir lo mismo en el caso de la incidencia, ya que estos datos están extrapolados para toda la población española desde registros poblacionales que representan a una minoría. En todo caso parece que la variabilidad provincial es muy baja. Así pues en su conjunto (hombres y mujeres) el cáncer colorrectal representa la primera causa de talidad por cáncer (segunda en los hombres tras el cáncer de pulmón y segunda en la mujer tras el cáncer de mama).

Es preciso destacar que según estos datos la mortalidad e incidencia del cáncer colorrectal son sustancialmente menores que las de otros países del norte de Europa, pero ya superior a la de Francia, Italia y Reino Unido.

Es muy relevante que en relación con el cáncer colorrectal se ha producido en los últimos años un aumento de su mortalidad e incidencia. Por ejemplo el número de muertes por cáncer colorrectal pasó de 2186 (hombres) y 2625 (mujeres) en 1975, a 2701 (hombres) y 2908 (mujeres) en 1980, a 3395 (hombres) y 3500 (mujeres) en 1985, a 4455 (hombres) y



4094 (mujeres) en 1990, a 5686 (hombres) y 4875 (mujeres) en 1995, y a 6591 (hombres) y 5380 (mujeres) en 2000.

En razón de lo anterior puede decirse que de la situación de privilegio que tenía España hace unos años hemos pasado a una situación de alerta que merece la pena analizar. Dos preguntas son claves: ¿qué ha cambiado en los últimos años para que se produzca este incremento en España?, y ¿qué se puede hacer para contener esta hemorragia de mortalidad por cáncer?

Los factores externos, especialmente la dieta son los grandes protagonistas, a lo que hay que añadir el sedentarismo y la obesidad como causas coadyuvantes para este incremento. La incidencia de estos factores externos se hace más patente aún en una población que va envejeciendo de manera llamativa. Envejecimiento y cáncer están muy relacionados, ya que el cáncer no es más que una proliferación anormal en la división celular, y todas las células disponen de un reloj biológico que controlan su división que con el tiempo se hace más sensible y delicado. A ello hay que sumar que la supervivencia de los pacientes con cáncer colorrectal es llamativamente mayor que hace años, lo que genera una mayor prevalencia de pacientes con cáncer y por tanto más cantidad de individuos con riesgo de morir por cáncer. El incremento producido en los últimos años en nuestro país en cáncer colorrectal es especialmente preocupante, y denota un cambio en la alimentación con mayor consumo de grasas, y menor de frutas y verduras. Por lo tanto la política que debe aplicarse debe ir orientada hacia la conservación de la dieta mediterránea, e incluirla en la educación infantil en las escuelas. En lo que se refiere al diagnóstico precoz del cáncer colorrectal la situación es muy compleja. Los objetivos para el Plan Integral de Cáncer serán

fomentar la realización de estudios piloto de cribado poblacional, utilizando sangre oculta en heces, que permita concluir la mejor estrategia de implantación de un programa de carácter poblacional. Al respecto es preciso tener presente que la detección de sangre oculta en heces presenta algunas limitaciones, como son una sensibilidad limitada, un valor predictivo bajo, una aceptabilidad escasa y en definitiva una participación poblacional baja. En lo que se refiere a la sigmoidoscopia y la colonoscopia es preciso recalcar que faltan estudios definitivos al respecto que muestren no sólo su rentabilidad sino su factibilidad y oportunidad. Sin embargo el Plan Integral de Cáncer establece que deberá hacer una revisión periódica de la evidencia científica para tener la agilidad necesaria en un cambio de estrategia sobre el cribado. Finalmente la supervivencia del cáncer colorrectal en España ha sido estimada por los análisis de los estudios realizados por los programas Eurocare 2 (1999) y Eurocare 3 (2003). En Eurocare 2 en España la supervivencia relativa a 5 años era de 47% para los hombres y del 50% para las mujeres (en Europa la media era del 48% para ambos sexos). En Eurocare-3 en España se ha pasado al 55% en hombres y al 56% en las mujeres (en Europa la media era del 49% y 51% respectivamente). Aunque estos resultados son alentadores es preciso decir una vez más que los datos provienen de los registros poblacionales existentes y que por tanto las cifras podrían estar sobreestimadas.

El cáncer colorrectal: un nuevo reto para la investigación clínica: El desarrollo de la investigación clínica en España ha sido espectacular en los últimos años, lo que ha sido debido por un lado al exce-



lente nivel de la oncología médica en España y por otro a la creación y desarrollo de los Grupos Cooperativos. En concreto el Grupo TTD (Tratamiento para los Tumores Digestivos) comenzó su andadura en 1986, constituyéndose como una asociación sin ánimo de lucro y con el fin de impulsar la investigación clínica en este campo. Hoy el grupo TTD tiene 15 años de historia, está constituido por 78 hospitales españoles y 121 investigadores, habiendo desarrollado 46 ensayos clínicos con un número de pacientes incluidos superior a 5000. Su impacto ha tenido repercusión nacional e internacional, y en la actualidad es uno de los grupos más activos del consorcio europeo de investigación en tumores digestivos, el grupo PETACC. El desarrollo de los grupos cooperativos españoles y concretamente el TTD ha sido tan impresionante que hoy no se concibe una investigación sólida su participación.

Sin embargo existen algunas amenazas. La Directiva Europea 2001/20/EC que será la base para el Real Decreto de 2004 establece en su artículo 19 que el promotor debe aportar todos los fármacos. Lo anterior plantea enormes dificultades para los grupos europeos clínicos (incluida la EORTC) para la promoción de los estudios por parte de los investigadores independientes, lo que sin duda limitará el desarrollo de nuevos esquemas e indicaciones de tratamiento. La pérdida de la independencia científica es algo grave y serio que preocupa a los investigadores, y que además debería preocupar a la sociedad y a la administración. Esperemos que finalmente prevalezca la cordura y se incluya en la nueva legislación la importancia de la investigación académica y de los grupos cooperativos.

Los grupos cooperativos tienen ante sí por tanto un nuevo reto, y desde luego una serie de oportunidades que debe aprovechar. Lo anterior pasa por el desarrollo de un plan estratégico que incluya el reconocimiento de estos grupos por parte de la administración (a través del Instituto Carlos III), la existencia de un apoyo económico oficial, y la reforma de la normativa europea sobre ensayos clínicos.

Absolutamente crucial ha sido la creación de la Red de Centros de Cáncer a través del proyecto de redes temáticas de investigación cooperativa del Instituto Carlos III. Esta iniciativa tiene como fin coordinar los investigadores a través de una red virtual en lugar de agruparlos en centros físicos, y en la que participan centros de investigación de cáncer, unidades de investigación de cáncer no hospitalarias y servicios clínicos de hospitales (la mayoría de Oncología Médica). En el momento actual en dicha red participan 25 hospitales y la vocación del Instituto Carlos III es su consolidación y que puedan incorporarse otras unidades que por el momento no están integradas.

El Plan Integral de Cáncer: Ante ésta situación el Plan Integral de Cáncer emerge como una excelente oportunidad. Dicho Plan se puso en marcha en Mayo de 2003 y debe terminar su redacción en Diciembre de 2003, para a partir de entonces comenzar el momento 0 que debe durar al menos 4 años. Sus características son: la de elaborar estándares y modelos básicos de atención para la prevención, detección precoz, tratamiento y rehabilitación de grupos de enfermedades (concepto integral); consensuar criterios sobre la forma de atender las patologías de manera integral y semejante en el conjunto del sistema nacional de salud; las comunidades autónomas



organizarán sus servicios según el modelo que más se adapte a sus peculiaridades y necesidades; y se elabora con la participación de las Sociedades Científicas y otros agentes sociales.

Sus objetivos son los siguientes: 1. Reducir las inequidades ante el riesgo de padecer cáncer, 2. Disminuir las variaciones injustificadas en el acceso a servicios preventivos y clínicos de calidad, 3. Lograr una mejor atención a los pacientes de cáncer *¡¡Centrada en el Paciente¡¡*, 4. Rehabilitar y reinsertar socialmente a quienes ya hayan desarrollado la enfermedad y, cuando sea el caso, paliar los sufrimientos de quienes lo han desarrollado, 5. Mejorar la información a pacientes, familiares, profesionales, gerentes y responsables políticos, 6. Fortalecer los sistemas de vigilancia y de información sobre cáncer, 7. Fomentar la investigación básica, aplicada y operativa para aumentar las oportunidades de evitar el cáncer y de tratar, rehabilitar y cuidar a quienes lo padecen.

Estos objetivos se deben alcanzar a través de las siguientes estrategias: 1. Elaboración de estándares y criterios que ofrezcan garantía de calidad, y basados en la evidencia científica disponible, 2. Garantía en la continuidad asistencial y en la fluidez entre niveles, servicios e instituciones. Optimización de redes asistenciales y diseño de vías clínicas de atención, 3. Monitorización de procesos, resultados y costes., 4. Promoción de la Investigación en todos los aspectos de la enfermedad, 5. Difusión, 6. Revisiones periódicas. (cada 2 años)

En cuanto a sus áreas de intervención son las siguientes: 1. Promoción de hábitos saludables y prevención de factores de

riesgo de cáncer en la población general 2. Detección precoz e identificación de personas con factores de riesgo de padecer cáncer 3. Asistencia a pacientes adultos con cáncer 4. Asistencia a pacientes pediátricos 5. Calidad de vida de los pacientes con cáncer 6. Cuidados paliativos 7. Sistemas de Información 8. Investigación.

La Investigación en el Plan Integral del Cáncer:

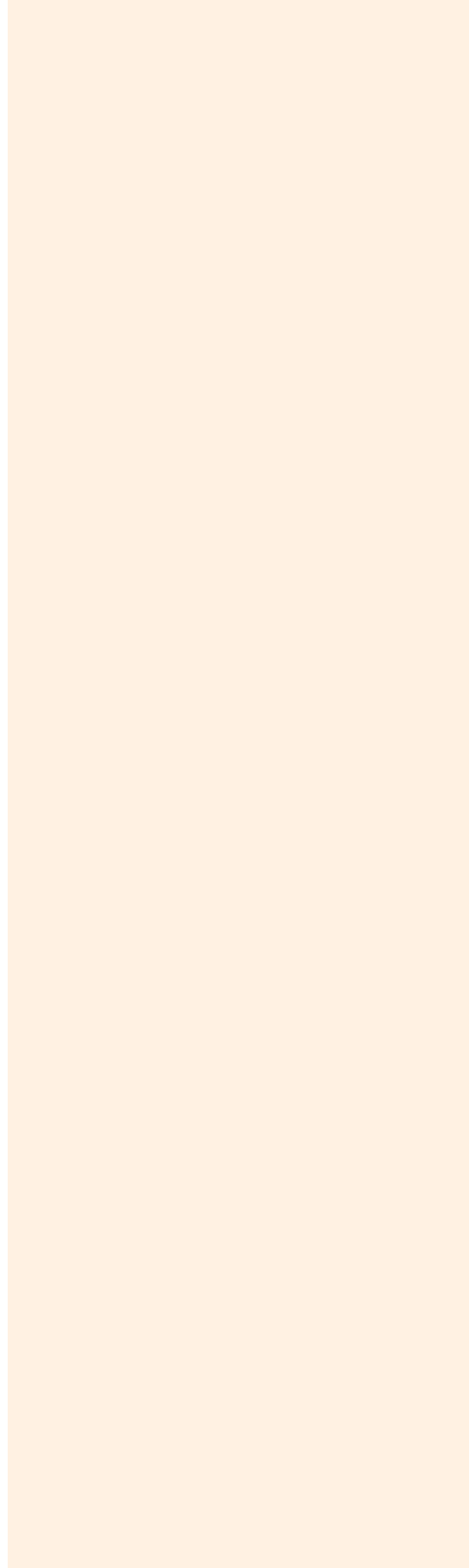
Una de las áreas prioritarias del Plan Integral de Cáncer es la investigación, que adquiere un carácter horizontal y transversal al abarcar todas las áreas posibles. El Plan Integral de Cáncer está llevando a cabo un análisis del estado de situación de la investigación sobre cáncer en España, y ha establecido como prioridades en investigación las parcelas básica, clínica, en salud pública y aplicada. Desde la consideración de diversos puntos críticos actualmente existentes, el Plan establece unos estándares de calidad y de promoción, con unos objetivos alcanzables pero muy ambiciosos que contempla desde una financiación adecuada, la carrera profesional, la consolidación de grupos estables, un contexto de colaboración entre la clínica y la básica, un sistema evaluador común y un esfuerzo en la comunicación con la sociedad. A través de estos presupuestos el Plan Integral de Cáncer establece unas líneas verticales y líneas horizontales de actuación. Todo ello conlleva una aproximación de la investigación en todas las áreas del Plan a la par que una aproximación desde los mecanismos moleculares más íntimos del cáncer hasta las nuevas estrategias terapéuticas.

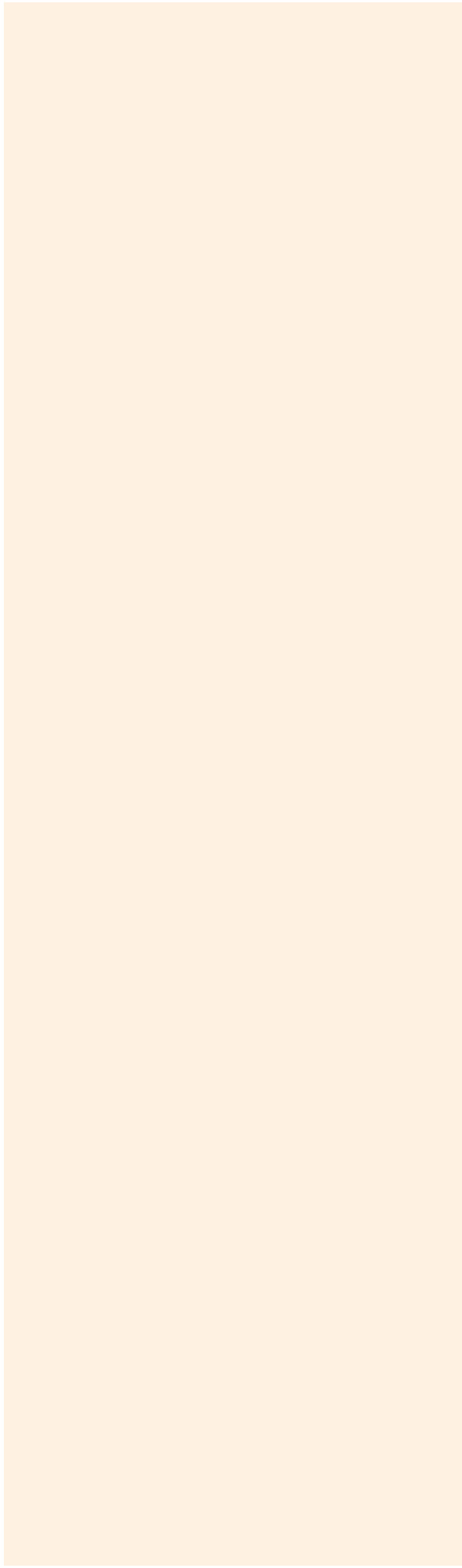
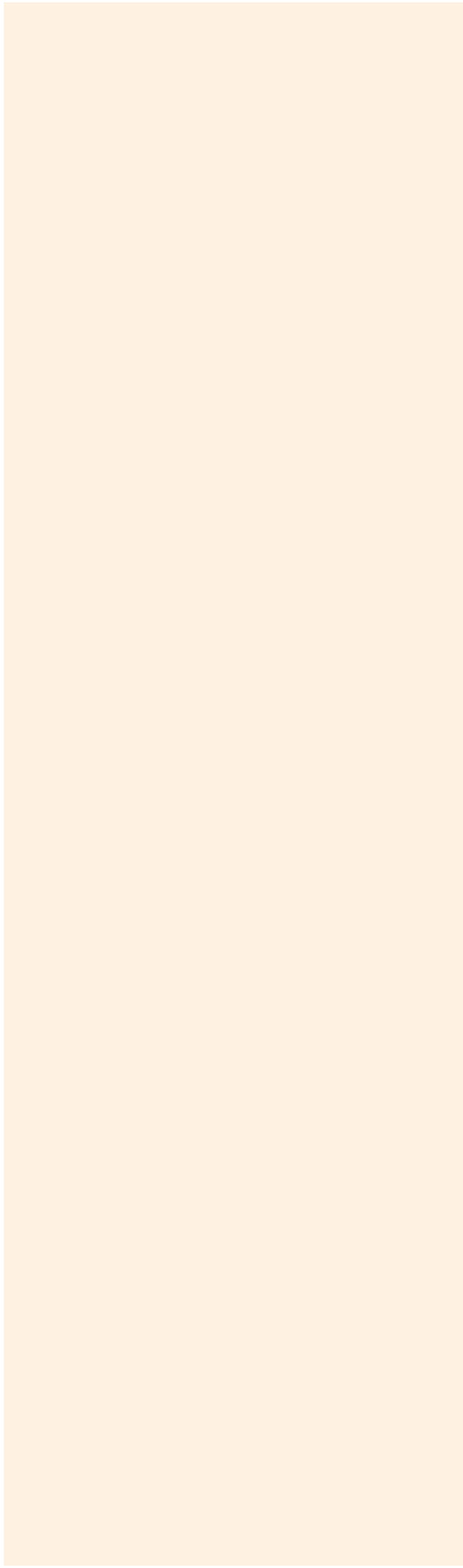
La repercusión de este Plan en el cáncer colorrectal será sin duda importantísima y una oportunidad única para reducir la incidencia y la mortalidad del cáncer colorrectal, mejorar sus tasas de supervi-



vencia a 5 años, y ofrecer un plan terapéutico individualizado dentro de un marco global donde participen todas las especialidades involucradas en el cáncer colorrectal en un ambiente de multidisciplinariedad.

NOTAS







Tratamiento quirúrgico de las metástasis hepáticas de cáncer colorectal

Joan Figueras

Hospital Universitario de Bellvitge,
Barcelona. *España*

RESUMEN

La cirugía continua siendo el mejor tratamiento para las metástasis hepáticas (MH) de cáncer colorectal. Sin embargo, la mitad de los pacientes operados presentarán una recidiva tumoral.

Es importante establecer unas recomendaciones útiles para la práctica clínica en el tratamiento de los pacientes con MH de CCR, basadas en los resultados de las mayores series publicadas hasta la actualidad.

Desde 1991 hasta 2002 hemos practicado 394 hepatectomías por MH CCR en 368 pacientes. Ni el número, tamaño (ni la invasión locoregional) fueron considerados criterios de exclusión. En 66 pacientes se indicó quimioterapia neoadyuvante y en 187 pacientes (62%) se instauró quimioterapia adyuvante. En 26 pacientes se llevó a cabo una segunda resección y en 33 se realizó destrucción por radiofrecuencia de las MH. En 30 enfermos fueron intervenidos de metástasis pulmonares.

La mortalidad postoperatoria fue del 3%. La supervivencia actuarial a 1, 3 y 5 años fue de 89%, 61% y 40% respectivamente. La supervivencia a 5 años de los pacientes que recibieron quimioterapia neoadyuvante fue del 39%, mientras que la de aquellos en quienes se resecaron metástasis pulmonares fue del 49% a los 4 años. En el análisis multivariante, el nivel de CEA preoperatorio > de 50 ng/ml, la presencia de cuatro o más MH, la presentación sincrónica, la enfermedad extrahepática y la invasión del margen de resección se mantuvieron como factores predictivos independientes de mortalidad. La administración de quimioterapia adyuvante obtuvo una mejoría significativa de la supervivencia.



CONCLUSIONES

Los pacientes con MH únicas o con < 4 nodulos, metacrónicas y que se pueden resear con una hepatectomia simple deberían considerarse quirúrgicos "de entrada".

En los pacientes con criterios de mal pronostico (≥ 4 nodulos, bilobulares, de gran diametro y sincrónicas) se debería realizar un estudio randomizado que estableciese el valor de la QT neoadyuvante.

A la espera de los resultados de los estudios randomizados en marcha, la Qt adyuvante debería considerarse el tratamiento estándar despues de la resección curativa de las MH.

El tratamiento con radiofrecuencia se está afianzando como la terapéutica ideal para los pacientes con recidiva de MH y con enfermedad bilobular.

Palabras clave: *Hepatectomía, Metástasis, Carcinoma colorectal, Supervivencia, Quimioterapia, Radiofrecuencia.*

ABSTRACT

Surgical resection of hepatic metastases (HM) of colorectal cancer is the only option for long term survival. But, half of the patient will present tumour recurrence after surgical resection.

To establish the efficacy of surgical resection of HM based on the results of the largest surgical series published nowadays in our country.

From 1991 till 2002, we have performed 394 hepatectomies in 368 patients for metastases of colorectal carcinoma. Neither the number nor the size of the metastases or the locoregional invasion were considered to be exclusion criteria. Sixty six patients underwent preoperative neoadjuvant chemotherapy and 187 (62%) postoperative adjuvant chemotherapy. In 26 patients a second hepatic resection was performed, 33 patients

underwent thermal ablation with radiofrequency, while in 30 patients a surgical resection of pulmonary metastases was also performed.

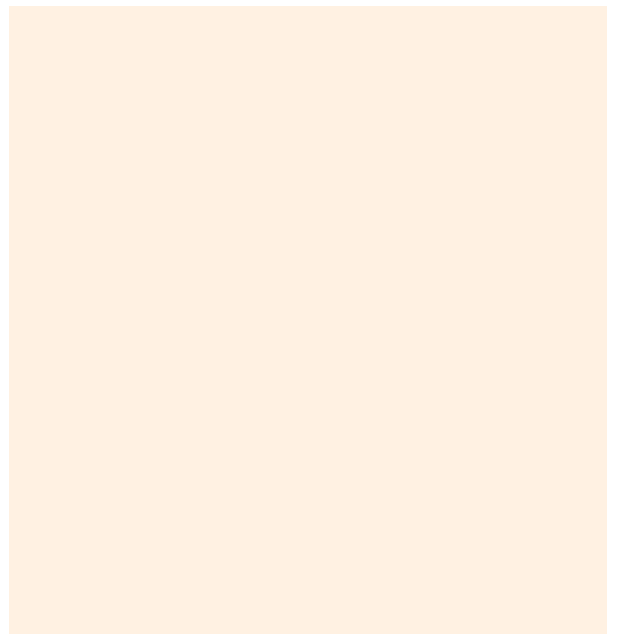
Postoperative mortality was 3%. One, 3 and 5 years actuarial survival rates were 89%, 61% and 40% respectively. Five-year survival of the patients that underwent preoperative chemotherapy was 39%, while the 4-year survival of patients with surgical resection of pulmonary metastases was 49%.

According to multivariate analysis: CEA levels >50 ng/ml, the presence of 4 or more metastases, synchronous presentation, extrahepatic disease and invasion of the resection margin were independent factors of bad evolution. Adjuvant chemotherapy improved survival significantly.

CONCLUSIONS

Resection of colorectal metastases associated with pre and postoperative chemotherapy, aggressive surgical indication, the systematic follow-up, the surgical rescue of hepatic recurrences with radiofrequency and curative intention and the adjuvant chemotherapy give a long place survival of 40%.

NOTES





Primary or secondary surgery of colorectal liver metastases

René Adam

Hepatobiliary Centre, Paul Brousse
Hospital. *France*

ABSTRACT

Liver resection remains the goal standard in the treatment of liver metastases from colorectal cancer and from a high proportion of other primary tumors. Two different situations should be considered in view of the initial resectability of the tumors.

In the case of metastases initially resectable with a potential of cure, liver resection is presently performed. Prognostic factors of recurrence are well-known and include mainly the number and size of metastases, the presence of extra-hepatic disease, the degree of invasion of the primary tumor and for some series the synchronous or metachronous pattern of metastases.

However, whichever the presence or not of factors of bad prognosis, liver resection should be considered because it remains the only chance of long term remission (5 year-survival: 30-40%) and sometimes of cure for the patients (1). Surgery should treat all the lesions since an incomplete treatment is not associated with a significant benefit in survival. Despite radical treatment, 60-80% of the patients will however recur, of whom 1/3 through isolated metastases of the liver. Repeat liver resection in these patients still gives a survival benefit of 30-40% at 5 years and should be considered in all the cases for which liver resection is potentially curative (2).

When liver metastases are initially irresectable, the strategy has been recently to convert them into resectable patients through neoadjuvant chemotherapy or adjuvant technical procedures.

The last few years have seen a great improvement in chemotherapy as first line treatment of irresectable colorectal liver metastases. Response rates achi-



eed with 5FU and Leucovorin have been dramatically improved by combination with Oxaliplatin and Irinotecan. The addition of Oxaliplatin has not only improved palliation for patients with metastatic colorectal cancer but has also been shown to downstage liver disease in patients with previously unresectable metastases. At the Paul Brousse Hospital, 95 out of 701 initially unresectable patients were found to be resectable on reevaluation (14%) and underwent a potentially curative resection which was associated with an overall 5 year-survival of 35%, similar to that reported for a priori surgical candidates (3). However, combination of chemotherapy and conventional surgery are sometimes insufficient to allow radicality of the treatment. When only a small anatomical part of the liver is free of tumors, and this part is insufficient to allow hepatic regeneration, after extensive hepatectomy, portal embolization may be indicated to induce an atrophy of the liver to be resected and an hypertrophy of the future remnant liver. By this way, some unresectable patients could benefit from a large resection with long term results similar to that of patients resected by a conventional approach (4). When multinodular bilateral metastases represent initial cause of unresectability, resection combined to cryosurgery or radiofrequency is able to rescue the patients for whom the residual tumors after a major hepatectomy resecting the highest amount of metastases, are limited in number (<3) and in size (<30mm). However, a complete treatment is sometimes impossible with a single procedure either because remnant tumors are too numerous, exceed 30 mm in size or are in close contact with remnant vascular or biliary structures.

In these cases, the choice should be oriented towards a two-stage hepatectomy provided that the overall strategy remains potentially curative (5). This strategy, often associated to prolonged chemotherapy or repeat liver resections, is heavy but it may offer a prolonged survival to some patients otherwise promised to a very poor outcome (3 year-survival : 30%).

In summary, the surgeon should presently integrate all these procedures so as to coordinate and adapt treatments to each individual patient, progressively extending the limits of resectability. By this way, we will be able to push back the frontier of the 10-20% minority of patients prone to be initial candidates to resection to a significantly higher proportion of patients.

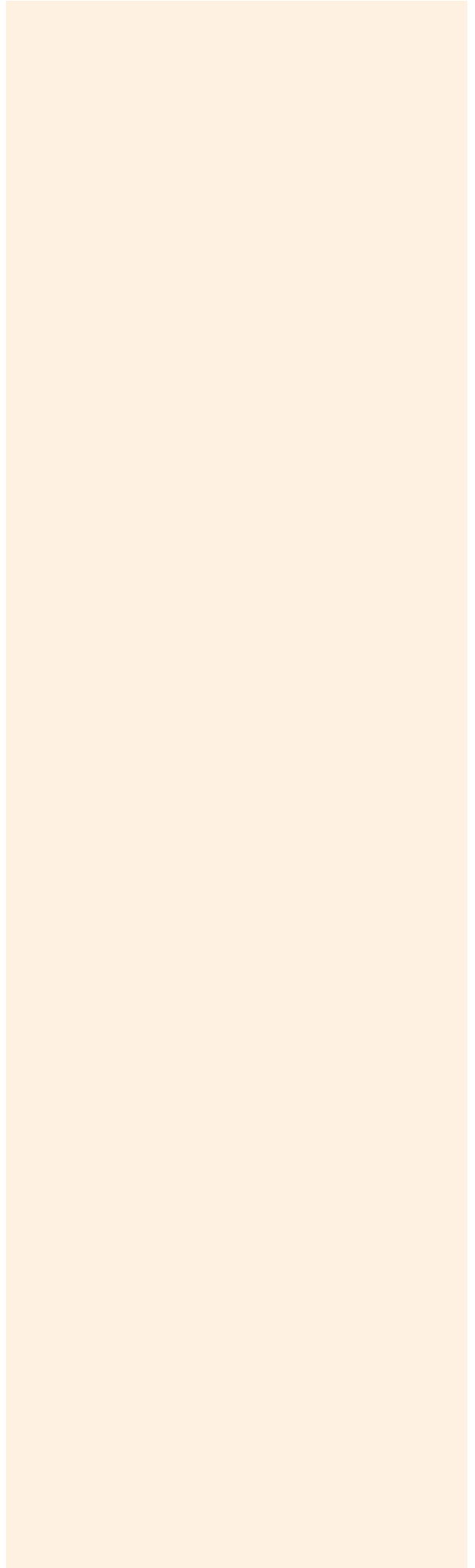
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NOTES







The role of radiofrequency ablation (rfa) in the treatment of liver metastases (lm).

ELIAS Dominique

Gustave Roussy Institute,
Villejuif. *France*

ABSTRACT

RFA is an efficient physical tool to destroy by heat LM, at condition to respect strict rules about the size of the tumors, their localization, and ballistic efficiency. So, the local recurrence rate is high (>20%) when the size of LM is greater than 30 mm and when it is sited close to a large vessel; the importance of the operator is thus fundamental.

Percutaneous RFA is restricted to unresectable LM (but the definition of unresectability is abnormally variable in the world), small-sized, less numerous than 4, well sited, and visible on ultrasonography or CT scan without injection. Because it does not allow to explore the abdominal cavity and perform intraoperative ultrasonography (and so, does not detect supplementary sites of cancer), its final results are far lower than those obtained with surgery. In our experience of more than 300 cases, the local recurrence rate was 9.9%, mainly for tumors >30 mm. Using concomitant chemotherapy should probably increase its efficiency. This mini-invasive technique had rare adverse events: mortality 1% (mainly on cirrhotic livers), and morbidity 10% (major : 3%, mainly liver abscess when there is a bilio-enteric anastomosis, stent or sphincterotomy). When there is a liver recurrence after hepatectomy, we showed that percutaneous RFA can replace repeat hepatectomy in 2/3 of cases, with the same late results as a more invasive repeat hepatectomy.

Intraoperative use of RFA (in combination with hepatectomy) allows treating with a curative intent almost twice as much patients as with surgery alone. RFA is mainly useful to treat small-sized (<30 mm), centrally sited tumors in the

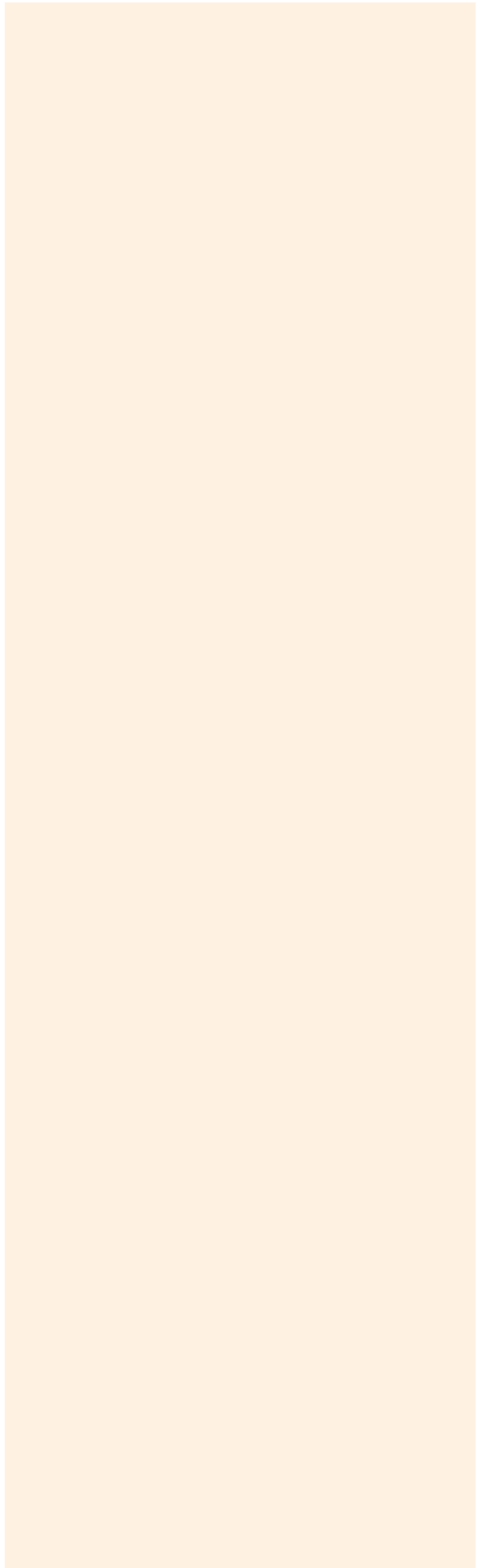


remaining part of the liver. Elective vascular clampings are possible and useful during this kind of RFA. We described the cooling of central bile ducts during RFA, which allows to successfully treat LM sited close to the biliary tree, and also the trans-RF hepatectomy where LM sited on the future line of transection of the liver are destroyed first with RFA before cutting through them. An analysis of 88 strictly unresectable patients (>5 LM, no sector of the liver respected, LM close to the central vascular structures) treated in IGR by hepatectomy plus RFA and chemotherapy was done. 582 LM were treated. Anatomic hepatectomy (n= 40) was used for large or contiguous multiple LM, wedge resection (n= 99) for small-sized superficial LM, and RFA (n= 227) for small-sized central LM. The median survival was 36 months for the 63 colorectal patients, exactly the double of 89 similar patients treated classically with i.v. chemotherapy (issued from the trial FFCD 96006). Even if the indication of anatomic, wedge, and RF resections were not the same in our series, the local recurrence rate was similar (6-7%) for the three procedures. This allows to conclude that RFA was as safe as wedge resection to destroy LM.

CONCLUSION

RFA is a safe, efficient and mini-invasive tool to treat small-sized LM. Its main advantage is to allow treating curatively an increasing number of patients. Its main disadvantage is its frequent application to wrong indications (large LM, resectable LM) because easy to perform and minimally invasive.

NOTES





The role of radiation therapy in the treatment of Esophageal Cancer

Bruce Minsky

Memorial Sloan Kettering Cancer Center, New York. **United States**

ABSTRACT

Historical series of external beam radiation therapy alone report 5-year survival rates of 0-10%. In general, radiation therapy alone should be reserved for palliation or for patients who are medically unable to receive chemotherapy. In the RTOG 85-01 randomized trial, patients with T1-4 primarily squamous cell cancers received 5-FU, Cisplatin and concurrent 50 Gy. The control arm was radiation therapy alone (64 Gy). Patients who received combined modality therapy (CMT) had a significant improvement in both median (14 months vs. 9 months), and 5 year survival (27% vs. 0%). With a minimum follow-up of 5 years, the 8 year survival was 22%. The incidence of local failure and/or persistence was also lower in the CMT arm (47% vs. 65%). INT 0123 was the follow-up trial to RTOG 8501 to test if higher doses of radiation were helpful. Patients with either squamous cell (85%) or adenocarcinomas (15%) were randomized to a slightly modified RTOG 85-01 CMT regimen with 50.4 Gy versus the same chemotherapy with a higher dose of radiation (64.8 Gy). For the 218 eligible patients, there was no significant difference in median survival (13.0 vs. 18.1 months), 2-year survival (31% vs. 40%), or local/regional failure and/or local/regional persistence of disease (56% vs. 52%) between the high dose and standard dose arms. Recent trials have used more novel agents such as paclitaxel, docetaxel, or Irinotecan based chemotherapy. Brachytherapy alone is as a palliative modality and results in a local control rate of 25-35% and a median survival of approximately 5 months. In the RTOG 92-07 trial, 75 patients received the RTOG 85-01 CMT regimen followed by a intraluminal boost. Local failure was 27% and the cumulative incidence of fistula was 18%/year and the crude incidence was



14%. Therefore, the additional benefit of adding intraluminal brachytherapy to radiation or combined modality therapy, although reasonable, remains unclear. In the adjuvant setting, randomized trials do not reveal a survival advantage with preoperative or postoperative radiation therapy alone (without chemotherapy).

A meta-analysis from the Oesophageal Cancer Collaborative Group also showed no clear evidence of a survival advantage with pre-operative radiation. There are 4 randomized trials comparing pre-operative CMT with surgery alone in patients with clinically resectable disease. The results are conflicting. Although this approach is reasonable, it remains investigational.

NOTES



Esophageal Cancer: Randomized phase III trial. Chemoradiation with and without surgery.

Michael Stahl

Kliniken Essen-Mitte, Essen. *Germany*

ABSTRACT

To determine whether surgery after chemoradiotherapy improves survival compared with chemoradiation alone in high risk patients with locally advanced SCC of the esophagus (uT3-4uNO-1M0), 184 eligible pts. were included into a German multicenter phase III trial until May 2002.

TREATMENT

Arm A: 3 cycles of 5-FU / leucovorin/ etoposide / cisplatin, followed by chemoradiation (cisplatin/etoposide + 40Gy), followed by surgery. Arm B: same induction chemotherapy, followed by definitive chemoradiation (cisplatin / etoposide + > 60Gy). Primary end point was overall survival, with the hypothesis of equivalence for both treatment arms at 2 and 3 years.

RESULTS

Complete treatment was performed in 65% of arm A and 85% of arm B pts., respectively. Median observation time reached 5 years. Mortality during chemo/chemoradiotherapy was 2.2% each in both arms. In-hospital mortality after surgery was 10.5%. Median survival time and three-year survival rate was 16 mos. and 28% (arm A) vs. 15 mos. and 20% (arm B), proving equivalence between the treatment arms ($p=0.04$). In pts. responding to induction chemotherapy 3-year survival was 45% vs. 44%, whereas in non-responding pts. it was 18% vs. 11% in arm A vs. arm B, respectively. Local tumor control at 2 years was 61% in arm A vs. 43% in arm B (log-rank $p<0.01$).

CONCLUSIONS

Surgery after preoperative chemoradiotherapy improves local tumor control in high-risk pts. with locally advanced SCC of the esophagus. However, multimodal treat-



ment was equivalent with regard to survival independent of whether pts. underwent chemoradiation and surgery or chemoradiation alone.

NOTES



Treatment of Locoregional Esophageal Cancer

Susan Urba

University of Michigan Medical Cancer
Center, Ann Arbor. **United States**

ABSTRACT

The treatment of loco-regional esophageal cancer has been a major focus of interest for investigators for many years. While metastatic disease has an extremely poor prognosis with median survival of 6 months, there is a small but definite percentage of patients with limited disease who appear to be curable. Therefore, most research efforts for this group of patients have involved combining several modalities of treatment, in an effort to improve upon the relatively poor survival rates achieved with surgery alone, which had long been the standard of care. Esophageal cancer is moderately responsive to radiation, but relatively insensitive to most chemotherapy agents. However, some chemotherapy agents act as radiosensitizers, providing rationale for the use of concurrent chemoradiation. A survey of community care practice patterns between 1988 and 1993 showed an increase in the use of chemoradiation instead of surgery as primary management of esophageal cancer (1).

What is the data that can help define what the current standards of care should be for these patients? Several large randomized trials have been conducted to explore issues regarding the multi-modality treatment of esophageal cancer. Eight of these trials will be summarized here, but unfortunately the true "standard of care" remains controversial, and in some cases the publication of new data has only served to complicate an already complex question. It is up to each individual physician to be aware of the data derived from the various trials, in order to be able to decide which treatment approach may be best for any given, individual patient.



Several questions to be explored include the following: what can be achieved by surgery alone? Does preoperative chemotherapy or chemoradiation add any survival benefit, or just additional toxicities? If a patient is treated with surgery, is there any role for post-operative adjuvant treatment? Is surgery necessary at all, or is definitive non-surgical therapy enough? What is the best non-surgical approach? After presenting the data that has resulted from the trials, some of the guidelines for treatment of esophageal cancer developed by the National Comprehensive Cancer Network (NCCN) will be summarized. The NCCN is a network of 18 cancer centers across the United States that has recruited panels of experts to create a series of treatment guidelines for various types of cancer. The panel on esophageal cancer has recently performed its yearly update of its practice guidelines.

SURGERY

Surgery for esophageal cancer typically entails a transhiatal esophagectomy or a standard transthoracic esophagectomy. When performed by experienced thoracic surgeons, peri-operative mortality is 5% or less. Typically, survival rates vary according to the stage of the disease. While five-year survival for all patients is 20-25%, the survival rate for Stage I disease is 60-70%, but only 5-10% for patients with Stage III tumors (1).

PREOPERATIVE CHEMOTHERAPY

Data from three trials that address the question of preoperative chemotherapy versus surgery alone have been published either in full manuscript or abstract form. Kelsen reported the results of a trial conducted by the Intergroup for 440 patients with potentially resectable carcinoma of the esophagus (2). They were

randomized to either surgery alone, or preoperative chemotherapy consisting of cisplatin 100 mg/m² on day #1, and 5-fluorouracil 100 mg/m²/day x 5 days. Treatment was administered every 4 weeks, for a total of 3 cycles. Surgery was performed 2-4 weeks later. Then, those patients whose disease had been responsive or stable after the preoperative regimen, received another 2 cycles of post-operative chemotherapy, with cisplatin being slightly reduced to 75 mg/m². Eighty-three percent of the patients assigned to preoperative chemotherapy received at least 2 cycles, but only 52% of those eligible to receive the post-operative chemotherapy received at least 1 cycle. Chemotherapy-related toxicity included 29% grade 3-4 neutropenia, 25% grade 3-4 mucositis, and 5 patients died of treatment-related causes, predominantly febrile neutropenia. Survival was not different between the 2 arms of the trial. Median survival for patients treated with preoperative chemotherapy was 14.9 months, and 16.1 months for those treated with surgery alone (p=0.53). At 1, 2, and 3 years, survival was 59%, 35%, and 23% for those treated with chemotherapy, and 60%, 37%, and 26% for those treated with surgery only. The authors concluded that surgery alone remains the standard of care for these patients.

In contrast, 2 other trials reported in abstract form have shown survival benefit to the administration of pre-operative chemotherapy. Clark reported the results of a trial conducted by the UK Medical Research Council in London (3). Eight hundred and two patients were randomized to receive surgery alone, or pre-operative chemotherapy consisting of 2 cycles of cisplatin 80 mg/m² and 5-fluorouracil 1000 mg/m²/day



x 4 days, given 3 weeks apart. No post-operative chemotherapy was attempted. Median survival was better for the group treated with chemotherapy- 17.2 months vs. 13.3 months, and 2-year survival was also better for the chemotherapy group – 43% vs. 34% ($p=.003$). The authors concluded that preoperative chemotherapy can improve survival for patients with resectable esophageal cancer, without serious adverse events.

How do we handle the conflicting results of these 2 randomized trials? Dr. Kelsen, the principal investigator of the Intergroup trial, compared both trials at the 2001 meeting of the American Society of Clinical Oncology. He concluded that both studies were large enough to be statistically sound, had apparently similar patient populations, and if anything, the chemotherapy in the British trial was less intense than in the American trial (2 cycles instead of 3, and no post-operative treatment.) There is no obvious difference between the trials that can clearly explain the different outcomes. He maintained that surgery or chemoradiation should continue to be the standard of care, and the possibility of performing a meta-analysis was suggested in order to resolve the question.

A 3rd trial has been reported in abstract form from the Netherlands (4), with positive results. One hundred sixty patients with squamous cell esophageal cancer were randomized to treatment with surgery, or preoperative chemotherapy consisting of cisplatin 80 mg/m² and etoposide 100 mg/m² IV on days 1-2 and 200 mg/m² p.o. on days 3-5, x 2 cycles. Patients who had a clinical response to the chemotherapy received an additional 2 cycles. At the time of

the report, median follow-up was a very short 15 months. However, median survival was 18.5 months vs. 11 months ($p=.002$), with benefit for the group treated with chemotherapy. Further follow-up is needed when data on 2 and 3-year survival is available.

A meta-analysis was performed in Hamilton, Ontario, Canada (5). Eleven randomized trials were analyzed, which included 1,976 patients. In the pooled data, the response to chemotherapy was 30%, and the histologic complete response was 5%. The odds ratio for survival at 1 year was 1.0 ($p=0.98$), and at 3 years was 0.77 ($p=0.48$). Therefore, pre-operative chemotherapy did not confer a statistically significant survival benefit for patients.

So, what does an oncologist do when confronted with a patient with loco-regional esophageal cancer? The NCCN guidelines maintain that surgery possibly followed by chemoradiation, or definitive chemoradiation possibly followed by surgery, are the 2 choices for operable T1-T3 tumors. Preoperative chemotherapy is not included in the recommendations. As in any instance of good patient care, the physician should assess the patient's tumor stage, physical stamina, potential ability to tolerate treatment, and wishes regarding therapy. Surgery remains one standard of care. For patients who desire an aggressive approach and have an excellent performance status, but cannot tolerate chemoradiation, some physicians may consider preoperative chemotherapy, realizing that one major trial supports this approach, but another does not. It is important to keep in mind that patients with Stage I disease have a relatively good survival with surgery alone and



could possibly be spared the toxicities of multi-modality treatment. Generally, more toxic treatments are considered for patients with more advanced disease whose prognosis is much poorer and may therefore justify the increased risks of therapy. The Intergroup trial and the Canadian meta-analysis provide the data supporting surgery alone as an effective treatment.

PREOPERATIVE CHEMORADIATION

Numerous randomized trials have addressed the issue of preoperative chemoradiation vs. surgery. However, several have been relatively small or have delivered the chemotherapy in a sequential rather than a concurrent fashion. This review will emphasize 4 relatively large trials that have compared concurrent chemoradiation vs surgery alone.

Walsh reported the results of an Irish trial in which patients with esophageal adenocarcinoma were treated with surgery or chemoradiation before surgery (6). The chemotherapy was 5-fluorouracil 15 mg/kg/day x 5 days, and cisplatin 75 mg/m² on day #7; 2 cycles were given in week 1 and 6. Radiotherapy was 40 Gy administered in 15 fractions over a 3-week period, beginning with the first course of chemotherapy. Surgery was performed 8 weeks after the initiation of the chemotherapy. One hundred fourteen patients were treated, and survival was improved for those who received chemoradiation. Median survival was 16 months vs. 11 months ($p=0.01$) in an intention-to-treat analysis; when the groups were compared on the basis of treatment actually received, the survival benefit was even greater for the chemoradiation arm - 32 months vs. 11 months ($p=0.001$). At 3 years, in intention-to-treat analysis, survival

was 32% for those treated with chemoradiation and 6% for those treated with surgery ($p=0.01$). While this survival difference is significant, the 3-year survival for those treated with surgery is unusually low, compared to almost any other surgical series. Also, the staging only included chest X-ray, abdominal ultrasound, and upper endoscopy, with CT scans performed only to clarify equivocal findings. The staging may have been sub-optimal according to more recent standards, with the possibility of unnoticed differences occurring between the arms of the study.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a multicenter trial to compare preoperative chemoradiotherapy followed by surgery to surgery alone in patients with Stage I and II squamous cell carcinoma (7). Two hundred eighty-two were randomized. The chemotherapy was 2 cycles of cisplatin 80 mg/m² given 0-2 days before radiotherapy, which was delivered in two 1-week courses, separated by two weeks. Five daily fractions of 3.7 Gy each were delivered, for a total of 18.5 Gy per course, and an overall total of 37 Gy. This split-course radiotherapy, with a relatively low total dose, can be considered less than optimal. There was no survival difference, with median survival of 18.6 months in both groups, and 3-year survival was about 36% for both groups. However, there were more post-operative deaths in the group treated with chemoradiation (16% vs. 5%) ($p=0.012$). The authors postulated that the high dose of radiation per fraction may have damaged lung tissue and caused severe immunosuppression in the peri-operative period. Fewer patients in the chemoradiation arm died of cancer (67%) than in the surgery arm (86%).



A trial performed at the University of Michigan compared a very intensive preoperative chemoradiation regimen to surgery alone (8). One hundred patients underwent randomization to surgery alone, or preoperative chemoradiation with cisplatin 20 mg/m²/day on days 1-5 and 17-21, 5-fluorouracil 300 mg/m² on days 1-21, and vinblastine 1 mg/m²/day on days 1-4 and 17-20. Radiotherapy consisted of 1.5 Gy fractions twice daily, 5 days a week, over 21 days to a total dose of 45 Gy. Transhiatal esophagectomy was performed on approximately day 42. Toxicities were substantial in the group treated with combined modality approach. Seventy-eight percent developed grade 3-4 neutropenia, 39% had neutropenic fever, and 63% required a feeding tube for nutritional support. At median follow-up of 8.2 years, there was no significant survival difference between treatment arms. Median survival was 17.6 months in the surgery arm and 16.9 months in the chemoradiation arm. Survival at 3 years was 16% and 30% respectively (p=.15). However, based on pilot data, this study was statistically powered to detect a relatively large increase in median survival from 1 year to 2.2 years, with at least 80% power. In multivariate analysis, the comparison of the effect of treatment arms on survival had a P value of .09, raising the possibility that there may be a mild trend for benefit of multimodality therapy, but since the study was powered to detect a relatively large difference in survival, a more subtle survival difference could not be detected. Of course, this is speculation, and the results of the study as it was conducted did not support an absolute benefit to preoperative chemoradiation. Multivariate analysis also showed that

tumors larger than 5 cm, squamous cell histology, and age greater than 70 years were independently associated with poorer survival.

A recently reported Australian trial randomized 256 patients to receive either cisplatin 80 mg/m² and 5-fluorouracil 800 mg/m²/day x 96 hours, concurrently with 35 Gy radiation (9). Neither endoscopic ultrasound or PET scan was used for screening. There was no difference in median survival, or survival at 3 years (p=.38). However, in a histology and gender subgroup analysis, preoperative chemoradiation was superior for females, and patients with squamous cell carcinoma, even though the numbers were relatively small.

So, again, these randomized trials show differing conclusions. A meta-analysis is in progress, conducted by the Meta-Analysis Group in Cancer, but until these results are available, what decisions should the practicing physician make? The NCCN guidelines do not include pre-operative chemoradiation in the recommendations for treatment of resectable disease, but rather recommend surgery or definitive chemoradiation. A few years ago, the U.S. Intergroup mounted a trial comparing preoperative cisplatin, 5-fluorouracil and concurrent radiation versus surgery alone. It intended to enroll more than 400 patients in a multi-institutional setting to definitively answer this controversial question for once and for all. Interestingly, the study had to be closed early because of lack of accrual. This had become an area in medicine where common practice evolved without the support of clearly definitive randomized data: so many physicians were treating patients



with pre-operative regimens that they were not enrolling patients in a study that included a surgery-alone arm.

As stated in the section above on Preoperative Chemotherapy, it makes sense to evaluate each patient individually. For healthy patients with good performance status, advanced tumor stage, and a desire to be treated in the most aggressive fashion, many physicians offer preoperative chemoradiation after a discussion with the patient regarding the lack of a clear consensus on the best treatment for patients with esophageal cancer. Elderly patients or those unable to tolerate the toxicities of chemoradiation would be treated with surgery.

POST-OPERATIVE CHEMORADIATION

Many patients are treated with surgery alone for their esophageal cancer. However, at the time of surgery, if the tumor is advanced or lymph node involvement is found, patients are often referred for consideration of post-operative chemotherapy and/or radiation. What is the data supporting this? A trial was recently conducted for patients with cancer of the stomach or gastro-esophageal (GE) junction. Since tumors of the GE junction are usually treated as esophageal cancer, the issues explored in that trial will be discussed here.

Macdonald reported the results of a multi-center study in which patients with resected adenocarcinoma of the stomach or GE junction were randomly assigned to surgery plus chemoradiotherapy, or surgery alone (10). Patients had Stage IB (tumor extending into the submucosa but involving 1-6 regional lymph nodes, or tumor invading the muscularis propria without lymph node

involvement) through IVMO disease (any large locally invasive tumors, or those with extensive regional lymph node involvement, without distant metastases). The adjuvant treatment was 5-fluorouracil 425 mg/m² plus leucovorin 20 mg/m² x 5 days, followed by 4500 cGy of radiation at 180 cGy per day, with fluorouracil 400 mg/m² and leucovorin 20 mg/m² given on the first four and the last three days of radiotherapy. One month later, 2 more cycles of the initial chemotherapy were repeated. A total of 556 patients were enrolled, and approximately 20% of patients had tumors in the GE junction. The adjuvant therapy was associated with a survival benefit. Median overall survival was 27 months for those treated with surgery alone, vs. 36 months in the post-op chemoradiotherapy group (p=0.005). Three-year survival was 41% in the surgery group, and 50% in the post-op chemoradiotherapy group. No specific subset analysis was performed for the patients with GE junction tumors, but the data did not appear to be different for this small group, compared to the other gastric tumors. The authors concluded that postoperative chemoradiotherapy should be considered for all patients at high risk for recurrence of adenocarcinoma of the stomach or GE junction who have undergone curative resection.

Therefore, when patients with tumors of the GE junction have undergone surgical resection as their primary treatment, it is advisable to treat them with post-operative chemoradiotherapy if their performance status is good and there are no other mitigating factors. The only exception would be patients with very early tumors. Accordingly, the NCCN



guidelines were recently updated to recommend that patients with adenocarcinoma of the distal esophagus who have undergone esophagectomy and have positive lymph nodes in the resected specimen should undergo post-operative chemoradiation, whereas adenocarcinoma of the proximal or mid-esophagus, or any squamous cell carcinoma, should simply be observed.

Patients with locoregional esophageal cancer are often treated with non-surgical therapy in the following situations: the patient is not medically fit to undergo surgery; the tumor would be technically difficult to resect; the patient has cervical disease which could require a laryngo-esophagectomy; the patient refuses surgery; the treating team of physicians have a preference for a non-surgical approach; or the treating institution does not have an experienced thoracic surgeon. If the decision is made to treat non-surgically, then concurrent chemoradiation should be used in preference to radiation alone. A multi-institutional trial headed by RTOG, with several other national study groups participating, was reported in 1992, and then a follow-up progress report was published 5 years later (11,12). One hundred twenty-three patients with locally advanced esophageal cancer were randomized to treatment with radiation only (64 Gy), or radiation (50 Gy) with 2 courses of concurrent chemotherapy, followed by 2 additional chemotherapy courses. The chemotherapy consisted of cisplatin 75 mg/m² and 5-fluorouracil 1000 mg/m²/day x 4 days, every 4 weeks during radiation, and every 3 weeks afterwards. With a minimum follow-up of 5 years, the median survival was 14.1 months and

5-year survival was 27% for the chemoradiation group, and median survival was 9.3 months, with no patients alive at 5 years, in the radiation alone group ($p < .0001$). An additional "confirmatory" group of 69 patients was treated with the chemoradiation regimen after the close of the randomized trial, and they had a similar outcome, with median survival of 17.2 months and 3-year survival rate of 30%. However, the toxicity of the regimens must be considered. Side effects were severe in 44% and life-threatening in 20% of those treated with combined therapy, as compared with 25% and 3%, respectively, of those treated with radiation alone.

For patients who are treated with a definitive non-surgical approach, chemoradiation clearly confers a survival advantage when compared to radiation, and should be the general treatment of choice. However, because of the substantial differences in toxicity, it is likely that some frail or medically compromised patients may not be able to tolerate combined modality treatment, and may have to be treated in a more palliative fashion with radiation alone.

No conclusive statement can be made regarding the superiority of chemoradiation followed by surgery vs definitive chemoradiation for patients with localized disease. A recent German trial was conducted to determine if surgery improved survival for patients with squamous cell carcinoma who were initially treated with chemoradiation (13). One hundred seventy-seven patients were randomized to receive either chemotherapy consisting of 5-FU, leucovorin, etoposide, and cisplatin, followed by chemoradiation (cisplatin/etoposide + 40 Gy), followed by surgery, or



the same initial chemotherapy, followed by definitive chemoradiation (60 Gy) without surgery. Median survival and 3-year survival were not significantly different: 16 mos vs. 15 mos, and 28% vs. 20% respectively.

Bedenne conducted a trial for 444 patients with locoregional disease who underwent 2 cycles of cisplatin and 5-fluorouracil concurrent with radiation (14). Patients who had a major response were then randomized to receive either surgery, or further chemoradiation. Only 259 of the patients treated with this regimen went on to randomization. Overall survival for both groups at 3 years was approximately 30% ($p=0.56$). While these results are of interest, the randomization of these patients did not take place immediately at diagnosis, but after they were treated with chemoradiation. Therefore, those who were unresponsive to chemoradiation were not included in the trial. This may well be the group who may benefit from surgery as part of the treatment regimen.

Recently, physicians involved in the U.S. Intergroup have explored the possibility of mounting a trial that would compare chemoradiation to chemoradiation followed by surgery. However, because of institutional biases one way or the other regarding the need to include surgery in the treatment regimen, it was concluded that it would not be feasible to accrue sufficient patients to complete a large randomized trial exploring this question.

CONCLUSIONS

It is very difficult to provide strict guidelines for the treatment of patients with locoregional esophageal carcinoma, because of the controversies and conflicting data described above. How-

ever, it is necessary to try to put current knowledge in perspective.

Surgery remains a standard of care for potentially resectable disease.

Definitive chemoradiation is a standard of care for locoregional disease, particularly if a patient is medically unfit for surgery, or if a thoracic surgeon experienced in esophagectomies is not available, or if the patient has cervical disease which would require very extensive surgery. Chemoradiation is superior to radiation alone for these patients. Some frail patients may only be able to tolerate palliative radiation.

Pre-operative chemotherapy is controversial, with two large randomized studies resulting in 2 different conclusions regarding survival benefit, and a meta-analysis showing no advantage to pre-operative chemotherapy. NCCN guide-lines do not include this as a standard of care.

Pre-operative chemoradiation is also controversial. One randomized trial showed a survival benefit for patients with adenocarcinoma, but the patients treated with surgery alone in that trial had an unusually poor outcome. A second trial showed no survival benefit. A third trial was negative but statistically powered only to reveal a large survival difference, and in multivariate analysis showed a possible trend to improved outcome. And the most recently reported trial showed a survival advantage only for patients with squamous cell carcinoma. The NCCN guide-lines suggest chemoradiation as a standard of care, to be followed with surgery in patients with a good response, particularly for adenocarcinoma of the distal esophagus. Physicians may consider offering this option to patients with advanced disease, excellent performance status, and who understand the contro-



versies and lack of consensus about the treatment of esophageal cancer.

Patients with adenocarcinoma of the gastroesophageal junction treated with surgery alone should have post-operative chemoradiation, particularly if there is tumor involvement in the lymph nodes.

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NOTES



Esophageal cancer: The role of PET scan in the clinical decision.

Sigrid Stroobants

University Hospital Gasthuisberg,
Leuven. **Belgium**

ABSTRACT

Esophageal cancer, especially adenocarcinoma, has been increasing in incidence over the past two decades in developed countries. Despite marked advances in surgical therapy and the introduction of combined treatment modalities, the overall survival rate of 10% or less at five years has not markedly improved. This is because these tumours continue to be diagnosed at an advanced stage in the majority of the patients. Furthermore, systemic and local recurrences are common even after multimodality treatment with curative intent. Improvement in overall survival in the future can only be achieved with the introduction of new, more potent chemotherapeutic agents and by a more appropriate selection of the treatment strategy for the individual patient. The latter is based on the ability to assess the correct stage of the disease at presentation and to discriminate responders from non-responders after neo-adjuvant treatment. The most commonly used conventional imaging modality is spiral computed tomography (CT) of the chest and abdomen. However it may underestimate the stage in > 40% of the cases, especially for T and N stage with reported accuracy's of only 50-60%. Also for the detection of M1 disease, it has been reported that CT missed 25% of the metastases later confirmed at surgery, mainly cervical or abdominal nodes and peritoneal implants. Since CT can not discriminate fibrotic or necrotic tissue from viable tumour, CT response after induction treatment does not adequately predict the pathological response. Endoscopic ultrasonography (EUS) is currently the most accurate non-invasive method for T and N staging with accuracy's of >90% for the T-stage and 65-80% for detection of nodal



involvement. However this technique is operator-dependent and is not applicable in patients with obstructive lesions. Positron emission tomography (PET) using the radiolabeled glucose analogue F-fluorodeoxyglucose (FDG) as a tracer is a well-established imaging technique that offers new perspectives in the staging of malignant disease. FDG-PET scanning enables the creation of metabolic images of tissues by studying the altered glucose metabolism in neoplastic cells. These images are complementary to the traditional morphologic images and may be more sensitive because the functional changes can precede the anatomical ones. Moreover FDG-PET scan offers the possibility to screen the whole body with one single imaging modality. This talk will review the experience of FDG-PET in the management of patient with esophageal cancer.

PREOPERATIVE STAGING

The presence of distant metastases constitutes the single most important prognostic factor. The median survival in these patients is only 6-12 months and cannot be prolonged significantly by any of the available therapeutic modalities. Since palliation can today be better and more safely achieved by non-surgical modalities, exclusion of distant metastases prior to surgery or neo-adjuvant therapy is mandatory. After conventional anatomical imaging, FDG-PET is able to detect additional metastasis in 6-20% of the patients mainly located in the cervical or abdominal nodes, liver or bone. Furthermore, PET proved to be helpful in the characterisation of equivocal lesions, although one has to be very cautious to exclude metastases in small lung nodules detected on CT.

In patients without distant metastases, the ability to perform a complete resection and the lymph node status are important prognostic factors. Careful assessment of the tumour, its location and relation to the surrounding structures will define the resectability. The imaging techniques of choice are EUS and CT. There is no indication for PET given its limited anatomical resolution. Lymph node status is the other important prognostic factor. Patients without lymph node involvement have a good prognosis. In case of lymph node involvement outcome decreases sharply but seems related to the number of lymph nodes involved. Up to 80% of patients have positive lymph nodes at surgery. Even in early T1b/T2 tumors, nodal involvement is common (30 – 50% of patients). This probably relates to the rich submucosal lymphatic network, leading to extensive and chaotic spread of tumour cells. None of the current imaging modalities today can reliably predict the presence of lymph node metastases. As in other tumour types, the accuracy of CT to detect nodal involvement is limited (45-75%) because size alone is not a good discriminator. EUS is more reliable because it not only evaluates nodal size but also their echogenicity and shape. Reported accuracy's are in the range of 65-90%. The major drawback of EUS is the fact that it can only be used in non-obstructive tumours and it is not able to evaluate nodes distant from the esophageal wall or behind air-structures (e.g. trachea). The performance of PET in detecting nodal involvement is location dependent. PET proved to be accurate in the detection of distant nodal involvement compared to CT, but was similarly insufficient but for the detection of regional lymph nodes. Due to the inten-



se uptake in the primary tumour combined with its limited anatomical resolution, the primary tumour and adjacent metastatic lymph nodes are seen as one mass. Maybe the use of combined PET-CT systems can overcome this problem. Another problem is the fact that often only minimal tumour load is found in metastatic nodes, which falls under the detection limit of current PET systems. In the study of Flamen et al. the performance of PET was compared to the combined use of CT and EUS in 42 patients who underwent surgery with extensive lymphadenectomy. The accuracy for diagnosing distant nodal metastasis was significantly higher for PET than for combined CT and EUS (86% vs. 62%, $P=0.0094$) based on both a higher sensitivity (77% vs 46%, $p=NS$) and specificity (90% vs 69%, $p=0.041$). For the detection of regional lymph nodes, CT+EUS proved to be more sensitive (83% vs 22%, $p=0.0026$) but less (45% vs 91%, $p=NS$) resulting in similar accuracy's (69% for CT+EUS vs 48% for PET).

RESPONSE ASSESSMENT AFTER NEO-ADJUVANT TREATMENT

Chemotherapy or combined radiochemotherapy is now increasingly performed prior to resection in patients with locally advanced esophageal cancer. A number of studies indicate that only patients who respond to this aggressive preoperative therapy have a long-term survival benefit from a subsequent resection, while morbidity and mortality of esophagectomy may be markedly increased in patients who do not respond to neoadjuvant treatment. Pre-therapeutic identification of patients who are likely to benefit from neoadjuvant therapy (response prediction) and assessment of response prior to surgery would therefore be helpful. However, none of the widely available cli-

nical staging methods and imaging techniques (including endoscopic ultrasound, CT scanning and magnetic resonance imaging) currently allows accurate response prediction or response evaluation. Preliminary results of FDG PET to evaluate response to induction treatment have been encouraging. A marked decrease in the tumor glucose uptake as compared to pretherapeutic levels was associated with a major pathological response and predictive for favourable outcome. PET was not able to discriminate major response from complete response due to false positive uptake in inflammatory tissue (mainly after radiation) or the inability to detect minimal disease. In the future, PET may be used as a guide to identify patients who should have resection after chemotherapy or radiochemotherapy.

NOTES





Cetuximab in the treatment of colorectal cancer

Josep Tabernero

Hospital Vall d'Hebron,
Barcelona. *España*

ABSTRACT

Cancer therapeutic antibodies encompass a diverse array of approaches and a number of mechanisms are involved in their mode of action. The rationale behind Monoclonal antibodies (MoAbs) is to target and kill antigen-expressing tumor cells while sparing antigen-negative normal cells. Antigens expressed on the surface of tumor cells provide the basis for this type of targeted therapy. These can be T- and B-cell expressed antigens (e.g., CD20), oncofetal antigens (e.g., CEA) or growth factor receptors (e.g., EGFR, HER-2/neu). In general, the antigens are tumor-associated rather than tumor-specific and are expressed at higher levels on malignant than normal cells.

There are three different MoAbs directed to the EGFR that are undergoing clinical development in colorectal cancer: Cetuximab (also called C-225 or Erbitux™), EMD 72000 and ABX-EGF. Cetuximab has demonstrated clinical activity in EGFR expressing tumors, either as a single agent or combined with chemotherapy. The main side effect is an acne-like rash that is seen in most patients, is not dose limiting and resolves without scarring on cessation of treatment. A relationship has been found between the severity of the rash and tumor response rate. In metastatic colorectal cancer, cetuximab in combination with 5-FU/FA/irinotecan yielded response rates of 48-63%. The recent results from the randomized phase II BOND study in patients with refractory metastatic disease showed response rates of 22.9% for patients receiving the combination of cetuximab and irinotecan, and 10.8% for patients receiving cetuximab as a single agent.

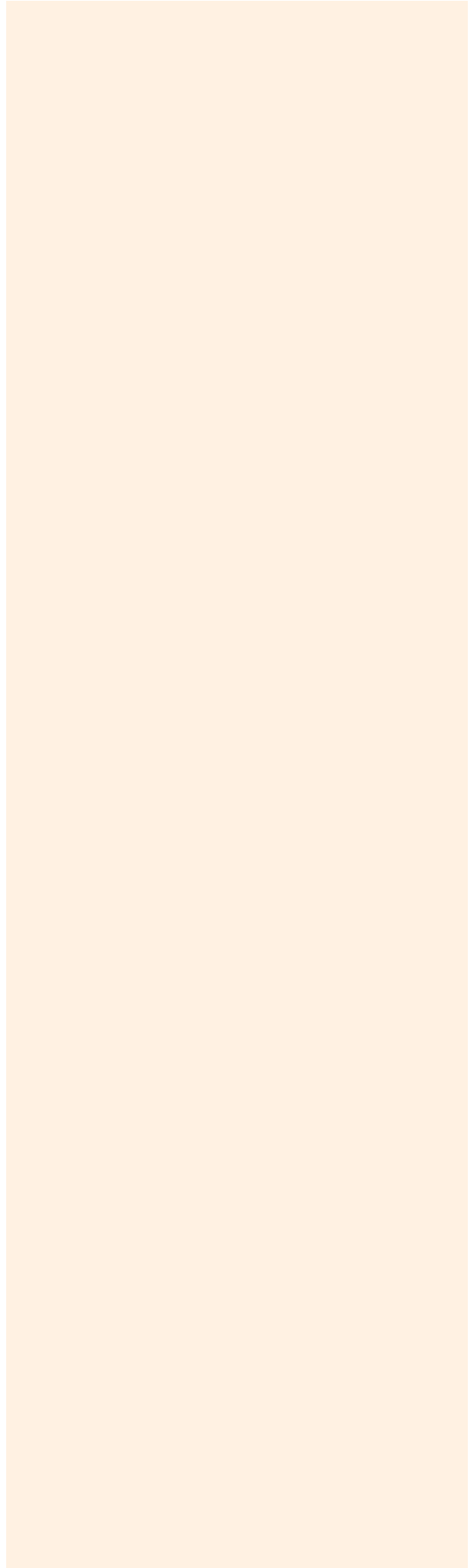


Cetuximab is undergoing clinical development in the first-, second- and third-line setting in patients with advanced colorectal cancer. Different chemotherapy schedules are being combined with cetuximab, either oxaliplatin-based like the FOLFOX4 schedule or irinotecan-based like the FOLFIRI or the AIO schedule.

There are several important challenging issues that might be addressed in the next years like the knowledge of the precise mechanisms of action, the most convenient schedule and the best tumor profile for optimal activity.

In summary, Cetuximab is clearly active against colorectal tumors that express the EGFR and it is undergoing a vast clinical development both as a single agent and in combination with standard chemotherapy regimens.

NOTES





Estado actual de otros anticuerpos anti-EGFR y de los inhibidores de tirosina quinasa de EGFR.

Andrés Cervantes
*Hospital Clínico Universitario,
Valencia. España*

RESUMEN

El factor de crecimiento de transformación alfa (TGFa) y su receptor específico, el receptor del factor de crecimiento epidérmico (EGFR), han sido implicados en el desarrollo y progresión de la mayoría de los tumores epiteliales humanos. La vía de transducción de señales a través de EGFR juega un papel fundamental en la proliferación de la célula tumoral, en la angiogénesis, en la diseminación metastásica y en la inhibición de la apoptosis. Además, TGFa and EGFR están sobrexpresados en muchos tumores humanos avanzados, por lo que el EGFR es una diana relevante para el tratamiento del cáncer.

Varios ensayos clínicos han mostrado que la inhibición del EGFR bloquea o detiene la proliferación de tumores humanos, sobre todo cuando se administran con quimioterapia o con radioterapia. Las terapias contra EGFR pueden clasificarse en dos grupos distintos: anticuerpos monoclonales e inhibidores directos de tirosina quinasa. Además de cetuximab (C225) conocemos estudios de otros anticuerpos monoclonales, como ABX-EGF, EMD 72000, MDX-447 and h-R3. Entre las moléculas de pequeño tamaño, que son inhibidores directos de tirosina quinasa (TKIs) se encuentran: ZD1839 (gefitinib), OSI-774 (erlotinib), CI-1033, EKB-569, GW-2016 y PKI166, entre otros. Estos dos tipos de fármacos tienen mecanismos de acción diferentes, pero producen al final una inhibición de la transducción de señales que parten del EGFR. Los estudios preclínicos nos muestran que los anticuerpos monoclonales se unen a la parte extracitoplásmica del receptor, en la zona donde debería unirse su ligando natural: el TGFa, impidiendo su unión, para de este modo inhibir la activación de la cascada de transducción de señales que dependen



de la actividad tirosina quinasa y estimulando la internalización del receptor. Por otra parte los inhibidores directos de tirosina quinasa bloquean la autofosforilación de este enzima en el EGFR. La mayoría de los compuestos anteriormente referidos se halla en fases de desarrollo inicial (fase I) o en fase II o III. Los distintos anticuerpos monoclonales desarrollados varían en su origen humano o murino, su afinidad por el receptor, sus variables farmacocinéticas y su especificidad o capacidad de unirse a otros receptores de la familia HER.

La clasificación más útil de los inhibidores directos de tirosina quinasa se hace según su mecanismo de acción, ya sea mediante una inhibición reversible o irreversible, o por la especificidad de la diana de inhibición (uno, dos o todos los receptores de la familia HER). Dos inhibidores directos de tirosina quinasa reversibles y específicos se encuentran en una fase avanzada de su desarrollo clínico: ZD1839 (gefitinib-Iressa) and OSI-774 (erlotinib-Tarceva). Datos clínicos muestran que estos compuestos tiene actividad antitumoral como fármaco único en pacientes de diferentes tipos de tumores sólidos. Otros compuestos se hallan en las fases más iniciales de su desarrollo.

Sin embargo, hay muchas áreas en las que la investigación va a ser fundamental para ahondar y resolver cuestiones fundamentales. ¿Qué grupo de pacientes puede beneficiarse más de esta aproximación terapéutica?. ¿Qué estudios biológicos nos pueden ayudar a definir de un modo más racional las dosis o los esquemas a utilizar?. ¿Cómo podremos caracterizar los parámetros de farmacocinética poblacional más útiles y las variables farmacogenómicas de mayor interés?. ¿Cuál es el contexto clínico más adecuado para el desarrollo de estos com-

puestos?. No sería de extrañar que en los próximos años estos productos pudieran enriquecer las posibilidades terapéuticas frente a distintos tumores humanos.

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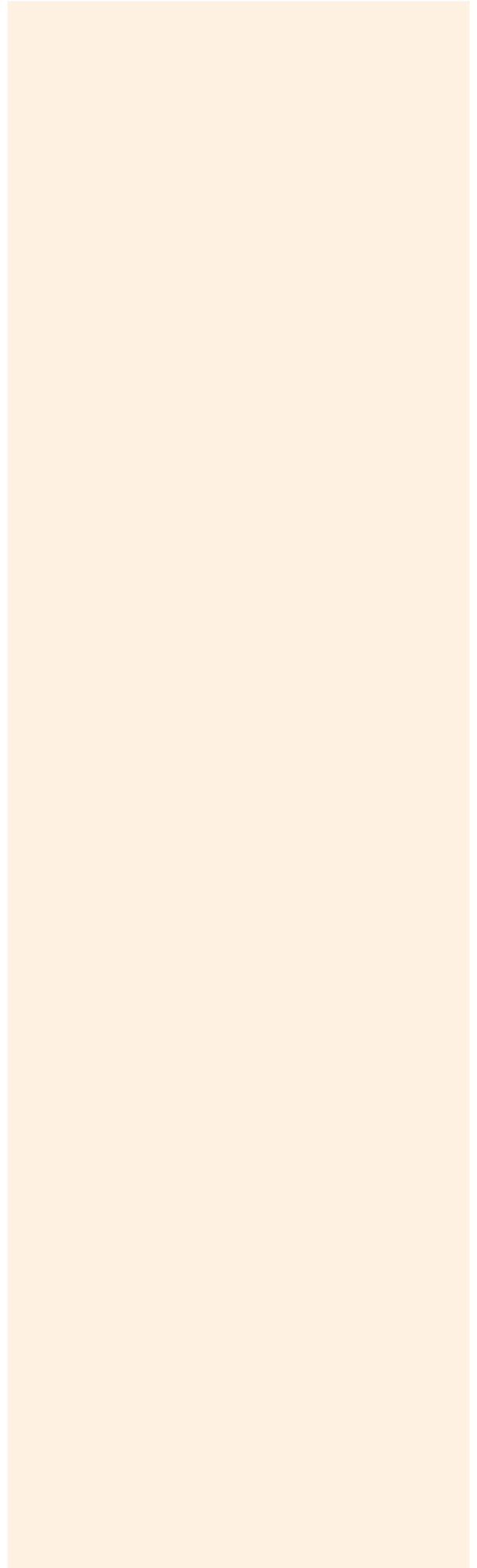
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NOTAS







Cox-2 inhibitors in the prevention and treatment of gastrointes- tinal tumors.

Ernest Hawk

National Cancer Institute,
Bethesda. **United States**

ABSTRACT

Cyclooxygenase (COX) -1 and -2 enzymes convert arachidonic acid into prostaglandins (PGs) and thromboxanes, thereby contributing to the carcinogenic cascade. Multiple solid tumors (e.g., colon, lung, prostate, breast, skin, esophagus, pancreas, bladder) over-express COX-2 and produce more PGs (particularly PGE₂) than healthy tissues from which they are derived. The precise mechanisms whereby COX-2 inhibitors may prevent cancer development are incompletely understood, but likely include: (1) reduction in arachidonic acid products, (2) prevention of free radical-induced genetic damage, (3) interference with the metabolic activation of carcinogens, (4) reduction of proliferation, (5) induction of apoptosis (i.e., restoration of growth regulation in transformed malignant cells), (6) immune-stimulation, and (7) antiangiogenic effects.

COX-inhibitors provide a paradigm for mechanistically-based anti-cancer agent development. Three complementary lines of research have established COX-2 as an important target for preventive or therapeutic intervention: (1) COX inhibitors -and COX-1 or COX-2 gene deletions specifically in some instances- inhibit intestinal carcinogenesis in both carcinogen-induced and genetically induced animal models (documented in more than 90 peer-reviewed scientific publications); (2) non-selective COX inhibitors reduce the incidence of colorectal adenomas, cancer, and cancer-associated mortality in human observational studies; (3) COX inhibitors regress pre-cancerous lesions (i.e., aberrant crypt foci and adenomas) in genetic and sporadic colorectal neoplasia cohorts (reported in more than fifteen uncontrolled and controlled studies). More limited epidemiologic data confirm



protective effects of NSAIDs in other GI cancers, particularly of the stomach and esophagus.

Recently, the field of cancer chemoprevention was invigorated by the success of a randomized, placebo-controlled trial sponsored by the NCI and Pfizer. This clinical trial tested a selective COX-2 inhibitor (celecoxib) in 83 persons with FAP, and showed that a 6-month intervention with 400 mg twice a day significantly reduced polyp number within well-defined areas by 28%, with 53% of treated subjects showing $\geq 25\%$ reduction. Significant improvement was also seen in the global colorectal and duodenal polyp status. These findings led to a new FDA approval of celecoxib to reduce the number of colorectal adenomas in persons with FAP, in conjunction with usual surveillance and surgical prophylaxis. Follow-up studies have been initiated to assess the relative effects of celecoxib in other FAP settings, including phenotypic suppression and adenoma regression in combination with other chemopreventive agents, such as eflornithine. Additional chemoprevention trials of celecoxib are ongoing in persons at risk for cancer due to HNPCC-related mutations, prior colorectal adenomas (at least 4 large phase III trials involving several thousand participants), and Barrett's dysplasia.

While initial prevention studies of COX inhibitors focused on the colon, non-selective COX inhibitors and COX-2 inhibitors have demonstrated pre-clinical preventive efficacy in several other extra-colonic tissues as well - particularly skin, bladder, aerodigestive, and mammary tumors. These data, coupled with evidence of COX-2 over-expression during carcinogenesis in a wide range of target

organs further support testing of COX-2 inhibitors in extra-colonic preventive settings. The NCI is currently exploring the chemopreventive efficacy of COX-2 inhibitors in esophagus, bladder, skin, prostate, and breast phase II/III clinical trials.

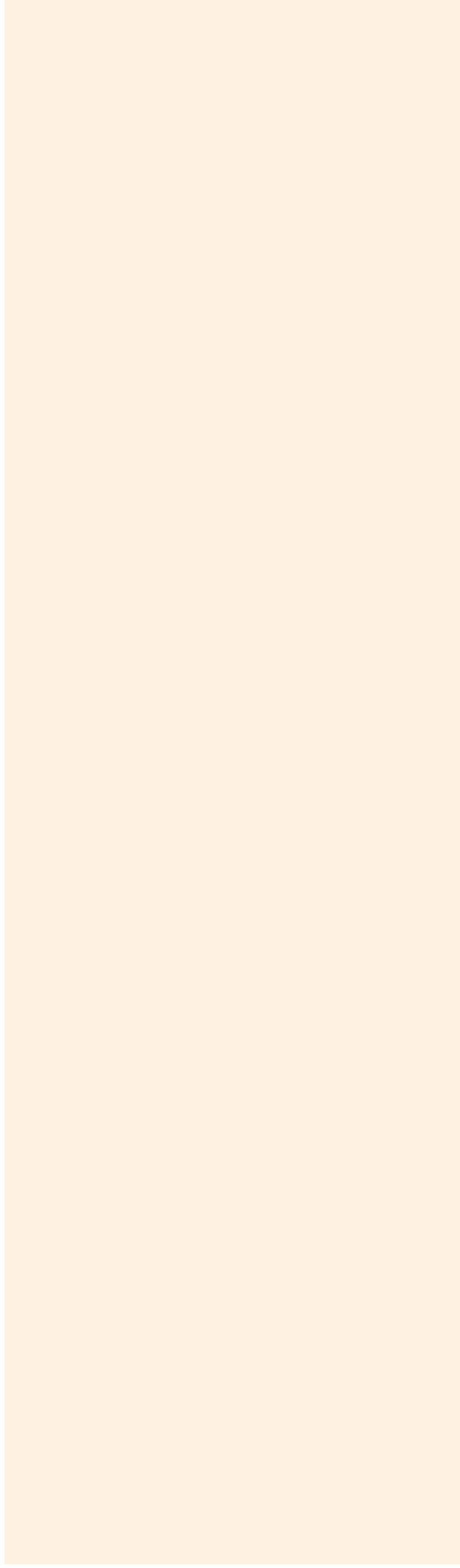
COX-2 inhibitors may play a significant role in cancer treatment as well. For example, Lundholm, et al., described improved survival in patients with metastatic solid tumors treated with indomethacin in the mid-1990's. More recently, COX-2 inhibitors have shown promise in cancer therapeutic settings in preclinical models; clinical trials to evaluate these effects are underway. For example, two small phase II trials have reported less severe neutropenia in patients using celecoxib in combination with IFL (irinotecan, 5-FU, leukovorin). The MD Anderson group recently reported a retrospective analysis of patients with metastatic colorectal cancer treated with capecitabine or a fluoropyrimidine in which they observed less hand-foot syndrome among patients receiving concomitant celecoxib. While these preliminary reports are promising, the usefulness of COX-2 selective inhibitors in GI cancer treatment cannot be determined until the results of several large ongoing trials are reported. For example, the VICTOR trial is a double-blind, placebo-controlled trial of rofecoxib 25 mg daily versus placebo in approximately 7,000 patients with stage II or III colorectal cancer without evidence of residual disease after surgery. This trial will follow patients for up to 5 years looking for changes in disease-free or overall survival. The EORTC is evaluating irinotecan/5-FU vs. irinotecan/capecitabine with or without celecoxib 400 mg bid in a 2x2 factorial



design involving patients with metastatic colorectal cancer. The NSABP will evaluate adenoma recurrence in patients randomized to celecoxib 400 mg BID vs. placebo in patients with stage I/II colorectal cancer. The PETACC (Pan-European Trials in Adjuvant Colon Cancer) Group has discussed a phase III trial of celecoxib over 3 years in patients with stage III colon cancer (e.g., following infusional 5-FU vs. bolus 5-FU vs. 5-FU with irinotecan or oxaliplatin per national standards). This trial would involve more than 1,400 patients and would focus on disease-free survival. Finally, preliminary work in pancreatic cancer patients suggests that COX-2 inhibitors may have activity in this disease as well, although an early study of celecoxib in combination with gemcitabine resulted in greater myelosuppression than anticipated. Additional studies are ongoing.

Perhaps most importantly, COX inhibitors offer several potential benefits beyond cancer including analgesia, cardiovascular prevention, and possibly preventive effects against cognitive disorders (e.g., Alzheimer's disease). Learning how to use NSAIDs, COX-2 selective inhibitors, or both optimally in persons at risk for these common diseases will be a challenging, though extremely rewarding, exercise.

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Bases teóricas para un tratamiento selectivo del cáncer colorrectal

Eva Martínez-Balibrea.

Hospital Universitari Germans Trias i Pujol, Badalona. España

RESUMEN

La oncología es una de las especialidades terapéuticas más desafiantes. Las células tumorales difieren sutilmente de las células del tejido del cual provienen y por tanto la mayoría de dianas terapéuticas se encuentran también en las células normales. Muchas de las quimioterapias actuales son capaces de erradicar las células malignas pero la mayoría tienen una modesta especificidad lo cual implica que se acabe dañando también a las células no tumorales. Además se considera que estos fármacos tienen un rango terapéutico estrecho, es decir, el ratio entre la dosis que se asocia con la eficacia antineoplásica y la dosis que se asocia con la toxicidad es relativamente pequeño. A todo esto debemos añadir que la mayoría de las veces, el tratamiento acaba fallando como consecuencia de la aparición de resistencia al fármaco. La situación ideal sería aquella en la que el oncólogo pudiera decidir el tratamiento en función de las características de cada paciente, de forma que pudiese saber de antemano cómo va a responder a una quimioterapia concreta en términos de eficacia y toxicidad. La farmacogenética estudia cómo las diferencias genéticas entre individuos pueden influenciar la variabilidad en la respuesta a fármacos. La experiencia clínica demuestra que esta variabilidad existe y por lo tanto es de suma importancia poder determinar las causas genéticas que determinan la respuesta a cada uno de los fármacos antineoplásicos. Los esfuerzos en descifrar el genoma humano nos han revelado que cerca del 100% de los genes contienen algún nivel de variación interindividual y se dice que son polimórficos. El 85% de estos polimorfismos son cambios en una sola base de la secuencia y se conocen como SNPs (Single Nucleotide Polymorphisms). Existen otros tipos de



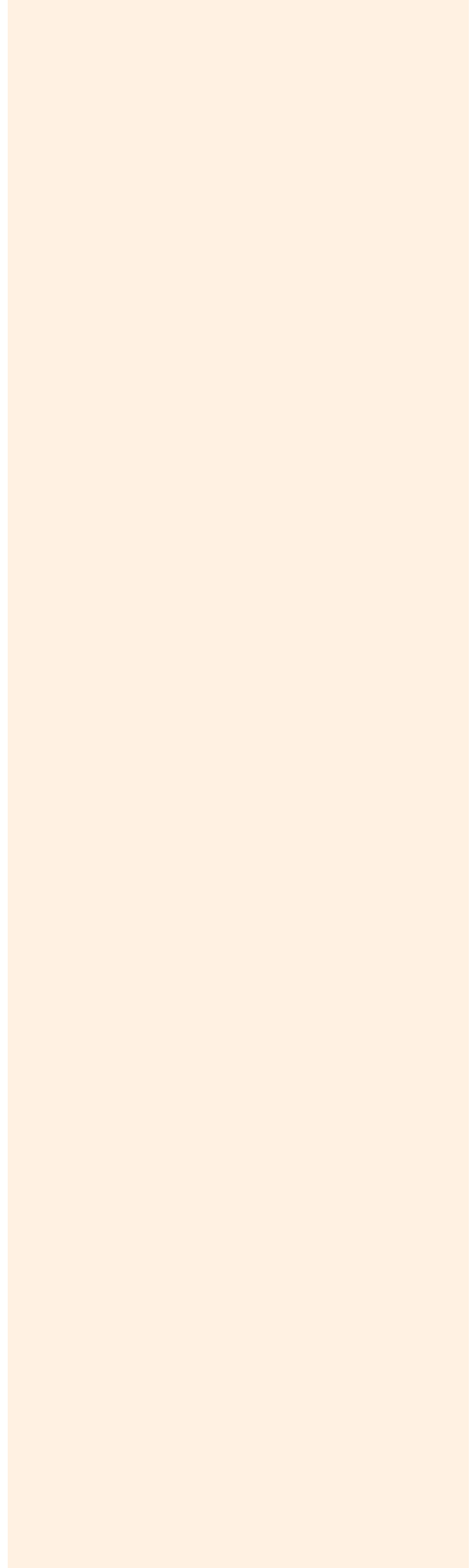
polimorfismos genéticos como son los de Longitud de fragmento de restricción (RFLP), Repetición en tándem de número variable (VNTR), o los microsatélites. Estas variaciones en la secuencia pueden ocurrir en regiones codificantes del gen o no codificantes y pueden afectar o no a la función de la proteína resultante o a su abundancia. Podemos encontrar polimorfismos en genes los productos de los cuales determinan la accesibilidad i/o detoxificación del fármaco, la eficacia y también la toxicidad. El tratamiento del cáncer colorrectal se basa en la utilización del 5-fluorouracilo (5FU), el CPT11 o Irinotecan y el Oxaliplatino. El 5FU es un análogo del uracilo que debe convertirse en 5-FdUMP para inhibir la Timidilato Sintasa (TS) que es la diana terapéutica. Diversos estudios han demostrado que una mayor o menor actividad de TS se asocia con una menor o mejor respuesta al 5FU. En la región promotora del gen que codifica la TS existe una zona de 28 pares de bases (pb) que se repite en tándem 2 ó 3 veces dependiendo del individuo. Un mayor número de repeticiones se traduce en una mayor expresión del gen y por lo tanto, los pacientes con un genotipo homocigoto de tres repeticiones tendrán una menor probabilidad de responder a 5FU (Pullarkat ST et al *Pharmacogenomics J.* 1:65-70; 2001). Más del 80% del 5FU se inactiva en el hígado a través de la enzima Dihidropirimidina Deshidrogenasa (DPD). Se sabe que el 3% de la población, aproximadamente, contiene una variación en la secuencia de uno de los dos alelos que reduce la actividad de la DPD y en consecuencia, cuando estos individuos son tratados con 5FU experimentan toxicidad a nivel hematopoyético, neurológico i gastrointestinal que en ciertos casos pueden ser fatales. El Irinotecan o CPT11 es un inhibidor de la Topoisomerasa de tipo I y

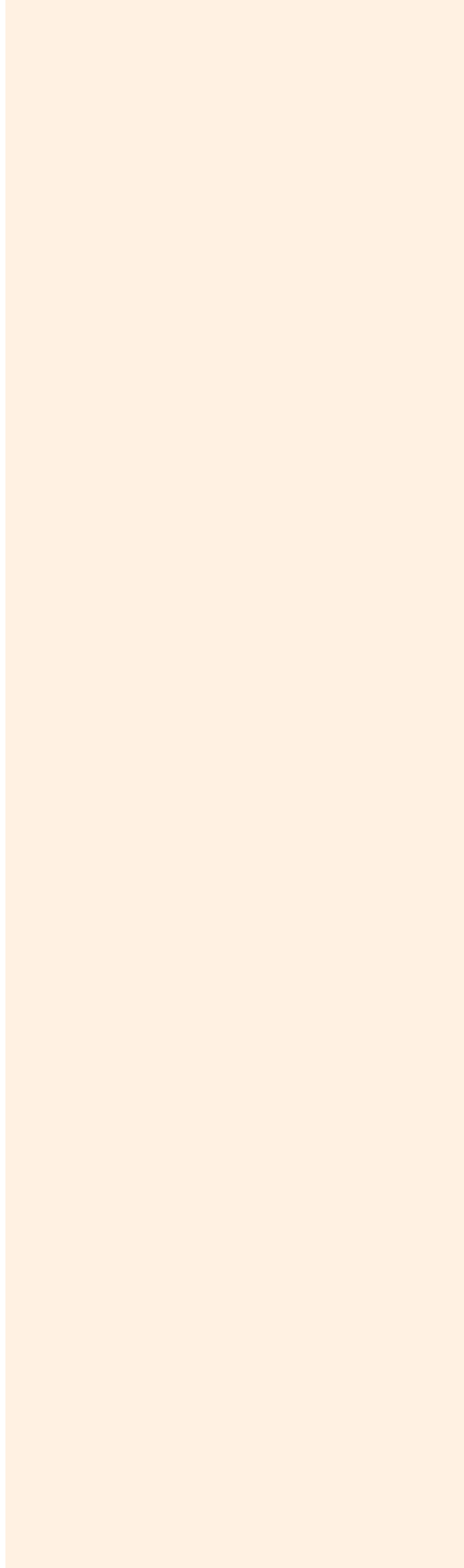
para efectuar su acción es necesario que se metabolice a SN38 que es el metabolito activo. La desactivación del SN38 ocurre en el hígado cuando la enzima UGT1A1 le transfiere una molécula de ácido glucorónico, facilitando así su excreción vía heces, bilis y orina. En el promotor del gen de la UGT1A1 también existe una zona importante para la transcripción génica cuya secuencia varía según los individuos. En este caso el polimorfismo consiste en 6 ó 7 repeticiones (aunque también se hayan descrito 5 y 8 en otras poblaciones) del dinucleótido TA lo que le confiere una menor actividad a la enzima a medida que incrementa el número de TA. En pacientes tratados con Irinotecan que sean homocigotos para el alelo de 7 repeticiones se producirá una acumulación de SN38 activo y podrán desarrollar diarrea y/o leucopenia con una mayor probabilidad (Ando Y et al. *Cancer Res* 24:6921-6; 2000). Los agentes platina-dos como el oxaliplatino actúan en mayor parte, dañando el ADN e interfiriendo así en la replicación y transcripción génicas. Algunas enzimas de las vías reparadoras presentan también polimorfismos genéticos que pueden hacer variar la acción de este tipo de fármacos. Entre otros, la proteína XRCC1 que participa en la vía .reparadora por escisión de bases, presenta un cambio de base en el codón 399 de una G por una A lo que conlleva a un cambio de aminoácido de Arginina a Glutamina. Este cambio se ha asociado con un decremento en la respuesta a oxaliplatino en pacientes tratados con este fármaco (Stoehlmacher J et al. *Anticancer Res* 21(4B) 3075-; 2001). Además de XRCC1 otras proteínas como XPD o ERCC1 (ambas de la vía reparadora por escisión de nucleótidos o NER) podrían también tener importancia en la selección del tratamiento con oxaliplatino. Existen muchas



otras proteínas cuyas secuencias génicas presentan polimorfismos y que también podrían ayudarnos a seleccionar mejor el tratamiento como son las Glutación transferasas (GST), la Metilén tetrahidrofolato reductasa (MTHFR), los citocromos p450, o la familia de transportadores de membrana ABC. Estos conocimientos pueden permitir la selección de los citostáticos más adecuados para cada paciente que vaya a ser tratado de un cáncer colorrectal. A esto hay que añadir que el crecimiento constante de las bases de datos de SNPs y otros polimorfismos nos proporcionan las pistas a seguir para encontrar cuáles son las variaciones verdaderamente importantes que nos conduzcan a un tratamiento selectivo y eficaz del cáncer.

NOTAS







The role of molecular markers in the adjuvant treatment of colorectal cancer

Wei Zhou

Emory University, Atlanta.

United States

ABSTRACT

Cancer is a genetic disease that requires the accumulation of multiple genetic alterations in oncogenes and tumor suppressor genes (TSGs) during tumorigenesis (1). Identification of the genetic alterations responsible for each tumor type is essential not only for the basic understanding of the disease but also for its diagnosis, prognosis and treatment.

Chromosomal loss identified by LOH analysis has also been associated with disease progression. However, these results are still controversial because most of these studies are retrospective, and existing traditional LOH methods are not reliable for archived clinical specimens. For example, some human tumors are defective in DNA mismatch repair (MMR tumors), and errors by the DNA replication machinery at microsatellites are not corrected. Consequently, new micro-satellites alleles are observed in these tumors, which makes LOH assessments problematic. More importantly and generally, larger alleles of microsatellites appear to be more susceptible to DNA degradation in tumors during apoptosis and necrosis.

The "counting alleles method" is a novel, SNP-based method, specifically designed for the analysis of allelic imbalance in fixed archived tissues (2). Genomic DNA is isolated and diluted to such extent that single molecules can be individually amplified in separate asymmetric PCRs. The presence or absence of genetic alterations is then determined by fluorescent probes. The allelic status of a sample is determined quantitatively by counting directly the number of paternal and maternal alleles in a sample, and evaluated by a statistical approach utilizing the sequential probability ratio test (SPRT).



An initial study using the counting allele technique involved 78 early stage colorectal cancer (CRC) patients. It revealed a correlation between 18q loss and vascular invasion in node-negative tumors (2). Subsequent analysis with 198 CRC patients demonstrated that early stage patients could be stratified into three groups with 0%, 27% and 48% chance of recurrence based on allelic status of 8p and 18q. Patients with early stage colorectal cancer typically have a good prognosis; however, 30 % of these patients develop recurrences and die from the disease (3). The ability to predict which of these patients might develop a recurrence would obviously be of great benefit for prognostication and treatment planning. The counting allele method is also suitable for the analysis of small tumors less than 2 mm in diameter, and we have evaluated allelic imbalance of chromosomes 1p, 8p, 15q and 18q in adenomas. Their results indicated that allelic imbalance occurs early during colorectal tumor development (4).

In summary, we would like to emphasize that a key advantage of "counting alleles" analysis is that the data output is in digital format, as it measures each parental allele separately. However, this advantage is partly counterbalanced by the requirement of hundreds of PCRs for analysis of each marker for a given sample, thus making it a low-throughput method. Therefore, this method is not suitable for genome-wide SNP analyses because of the cost and labor involved. Yet, this method is amenable to automation and suits well for study of a defined molecular target for disease diagnosis or prognosis.

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Pharmacogenomics in Colorectal Cancer

Heinz Joseph Lenz

Norris Comprehensive Cancer Center,
Los Angeles. *United States*

ABSTRACT

The goal in administering chemotherapeutics is to develop the ability to predict the outcome of therapy in terms of response and toxicity. Technology has been developed to allow tumor profiling with measurement of protein expression and gene expression levels of markers and even genetic polymorphisms, that may predict response to particular chemotherapeutics. The chemotherapeutics for which particular markers have been shown to predict outcome include the fluoropyrimidines and platinum. The next step is to develop clinical trials which will prospectively assess the benefits of profiling a patient's particular tumor which should translate into an improvement in response and toxicity.

A major challenge in administering chemotherapeutics to cancer patients is predicting the outcome of therapy in terms of tumor response and toxicity. Pharmacogenetic variability in drug-metabolizing enzyme systems is a major determinant of variations in these outcomes. Accordingly, the goal of pharmacogenetic screening prior to chemotherapy is to identify patients who might respond to particular chemotherapeutic agents and also those patients who might experience increased toxicity with these same agents. Because anticancer agents generally have a narrow margin of safety, the role of molecular pharmacogenetics in cancer chemotherapy is critical.

Many genes are targets of drugs that are biotransformed to active compounds by enzymes that exhibit genetic polymorphism or are expressed differently in tumors vs normal tissue. Further, certain anticancer drugs are detoxified by polymorphic enzyme systems. Most significant



is the fact that most cancer drugs exhibit interpatient variability in pharmacokinetics and toxicity. Thus, the goals of therapy should be to choose anticancer drugs based on the profile of a particular patient's tumor, hence maximizing potential response to therapy and minimizing toxicity.

Prognostic markers predict a tumor's growth potential or ability to metastasize, while predictive markers suggest how effective a particular chemotherapeutic agent will be in a specific patient. A clear role for prognostic and predictive markers in chemotherapy however has yet to be delineated. We will attempt to develop a role for these markers by reviewing the development and application of molecular markers and their application in gastrointestinal tumors.

A substantial amount of data has been published about thymidylate synthase (TS) and its potential application as a marker, both in the adjuvant and metastatic settings, for patients receiving fluoropyrimidine-based chemotherapy. In our research, we have identified other potential predictive markers of response and survival to both fluoropyrimidines and platinum-based chemotherapeutics. These markers include thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) as prognostic and predictive markers for fluoropyrimidine chemotherapy, and the application of excision repair cross-complementation group 1 (ERCC1), XPD, and glutathione S-transferase P1-1 (GSTP1-1) for platinum-based therapy.

It is critical to understand the regulation of genes to identify better targets for chemotherapeutic agents. Unfortunately,

the regulation of TS expression is still not very well understood. In my laboratory, we hypothesized that a 28 base pair repair repeat in the 5' UTR region of the promoter region could be a binding site for a not yet identified transcription factor. In vitro data demonstrated that in a CAT assay a triple repeat of this 28 base repair was associated with higher TS activity (Hiro et al 1996). We hypothesized that patients with a genomic polymorphism in the 5' UTR of TS would predict intratumoral gene expression and therefore clinical outcome. In a study of 52 patients we determined the genomic polymorphisms in the blood of these patients and compared it with TS gene expression levels in liver metastases from colon cancer and in normal liver (Pullarkart et al 2001). Our data confirmed that patients with a triple repeat had significantly higher TS gene expression in the tumor, as well as in the normal tissue, and that this was associated with response and clinical toxicity in patients treated with protracted infusion of 5-FU. For the first time, a genomic polymorphism was linked with intratumoral gene expression, as well as clinical outcome and toxicity (Pullarkart et al 2001, Park et al 2002). Our data were confirmed by other groups, showing that patients with a triple repeat had a significantly less downstaging to chemoradiation therapy (Villafranca et al 2001). With these findings, our group established that genomic polymorphisms may become an important tool to predict clinical outcome and toxicity.

More significantly, we recently identified the transcription factor that specifically binds to this double/triple repeat (Mandola et al, Cancer Res June 1, 2003). This transcription factor may be a more successful target for the treatment of



GI cancers. We also found a novel genomic polymorphism within this repeat which alters the binding of the newly identified transcription factor and determines the intratumoral gene expression and allows the prediction of response and survival to 5-FU based chemotherapy.

There have been no clear molecular correlates for the efficacy of radiation therapy or for the risk for pelvic recurrence in patients treated with chemoradiation therapy. We studied 120 patients with rectal cancer treated with neo or adjuvant chemoradiation therapy. We measured intratumoral gene expression levels and genomic polymorphisms of genes involved in the 5-FU pathway as well as DNA repair, angiogenesis and apoptosis. We were able to show that gene expression of TS, DPD, ERCC-1 and VEGF in the normal adjacent tissue predicted pelvic recurrence. In addition the genomic polymorphisms in the EGFR and GST-P1 were significantly associated with recurrence in patients with rectal cancer.

Our success in predicting outcome and toxicity in patients treated with 5-FU, led us to expand our research onto metabolic enzymes in the platinum pathway. We already had published that gene expression levels of ERCC-1 were predictive of response and overall survival in patients with locally advanced gastric cancer treated with 5-FU and cisplatin (Lenz et al 1996). This was the first report of molecular markers predicting clinical outcome in gastric cancer. We were interested in establishing a genetic and genomic profile that would predict efficacy of oxaliplatin chemotherapy in patients with colorectal cancer. We showed for the first time that ERCC-1 and TS gene expression predicted overall

survival in patients with colorectal cancer in second/third line chemotherapy (Shirota et al 2001). This was the first report of intratumoral gene expression measured in paraffin-embedded tissue sections.

Recently, we completed a retrospective study of over 200 patients treated with 5-FU/oxaliplatin chemotherapy in second line. In this patient population we were able to show that a genomic polymorphism in ERCC-1 was associated with intratumoral gene expression and overall survival for patients treated with 5-FU / oxaliplatin therapy. We included other genes involved in the platinum pathway and established four genomic polymorphisms (TS, ERCC-1, GST-P1, XPD) which were independent markers of overall survival and/or response to second line chemotherapy presented in the oral session at ASCO 2002. Patients who have none of the four favorable polymorphisms had a median survival of 5 months, patients with one of these four favorable polymorphisms had a median survival of 10 months, and patients with 2 or more of these four favorable polymorphisms had a median survival of 18 months ($p < 0.001$) (Lenz et al, ASCO 2002).

With the development of new effective anticancer drugs such as oxaliplatin, avastin and cetuximab, it is of clinical significance to better understand the metabolism and the mechanism of resistance of these new active agents. It is essential to understand why some patients develop life-threatening toxicity and why some tumors are resistant to these novel agents.



NOTES

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Farmacogenómica y cáncer colorectal. Experiencia del Grupo TTD

José Luis Manzano Mozo

Hospital Universitari Germans Trías i Pujol. Badalona. España

RESUMEN

Con las bases teóricas y clínicas de la literatura, y la experiencia de uno de sus centros sobre el impacto que algunos polimorfismos genéticos pueden tener en la actividad de determinados citostáticos, el grupo TTD acordó en 2001 un proyecto de farmacogenética, basado en los polimorfismos genéticos directamente relacionados con los fármacos más activos en CCR y conocidos entonces. El proyecto se basa en la determinación de los polimorfismos genéticos de TS, XRCC1 y UGT1A1, y se distribuye en 2 fases. La primera fase consiste en la determinación de los polimorfismos para el análisis de su influencia en la respuesta al tratamiento. Incluye la confirmación de la experiencia de uno de los centros, y la determinación en todos los pacientes que se incluyen en los ensayos clínicos que el grupo TTD está desarrollando. Si los resultados de la primera fase son favorables, la segunda fase consistirá en el desarrollo de un ensayo de fase III comparativo, aleatorizado con un grupo de tratamiento estándar frente a un grupo en el que se seleccionará el tratamiento según los polimorfismos que presente el paciente.

Los primeros resultados corresponden a la experiencia de un solo centro. Se trata del análisis de TS, XRCC1 y UGT1A1 de manera combinada en un grupo de 73 pacientes tratados con poliquimioterapia por CCR avanzado y metastásico con masas medibles. Los resultados no muestran diferencias en respuestas objetivas cuando se compara la combinación de los polimorfismos (TS, UGT1A1 y XRCC1) entre tenerlos favorables o desfavorables. Tampoco aparecen diferencias cuando se analiza el polimorfismo de la TS únicamente. El análisis combinado de los polimorfismos de los pacientes en progresión



Figura 1: CCR Tiempo a la progresión según polimorfismos genéticos TS, XRCC1, UGT1A1 en CCR (73p)

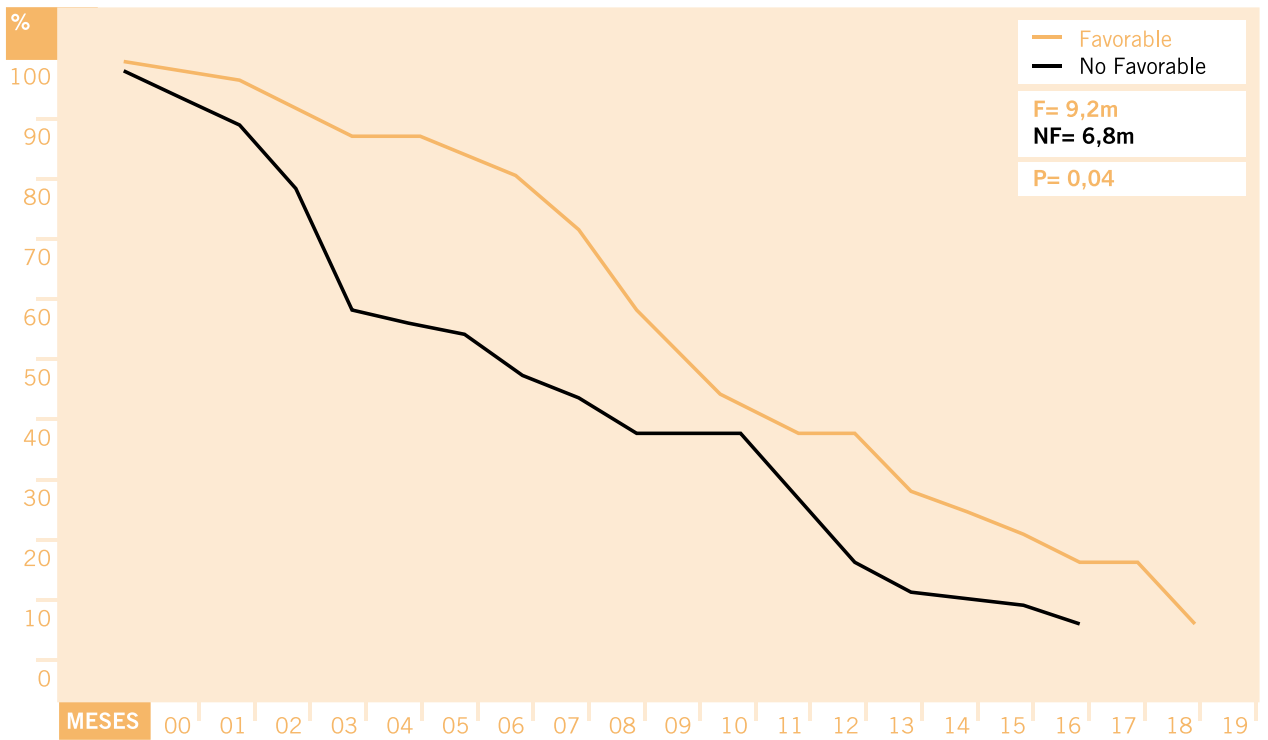
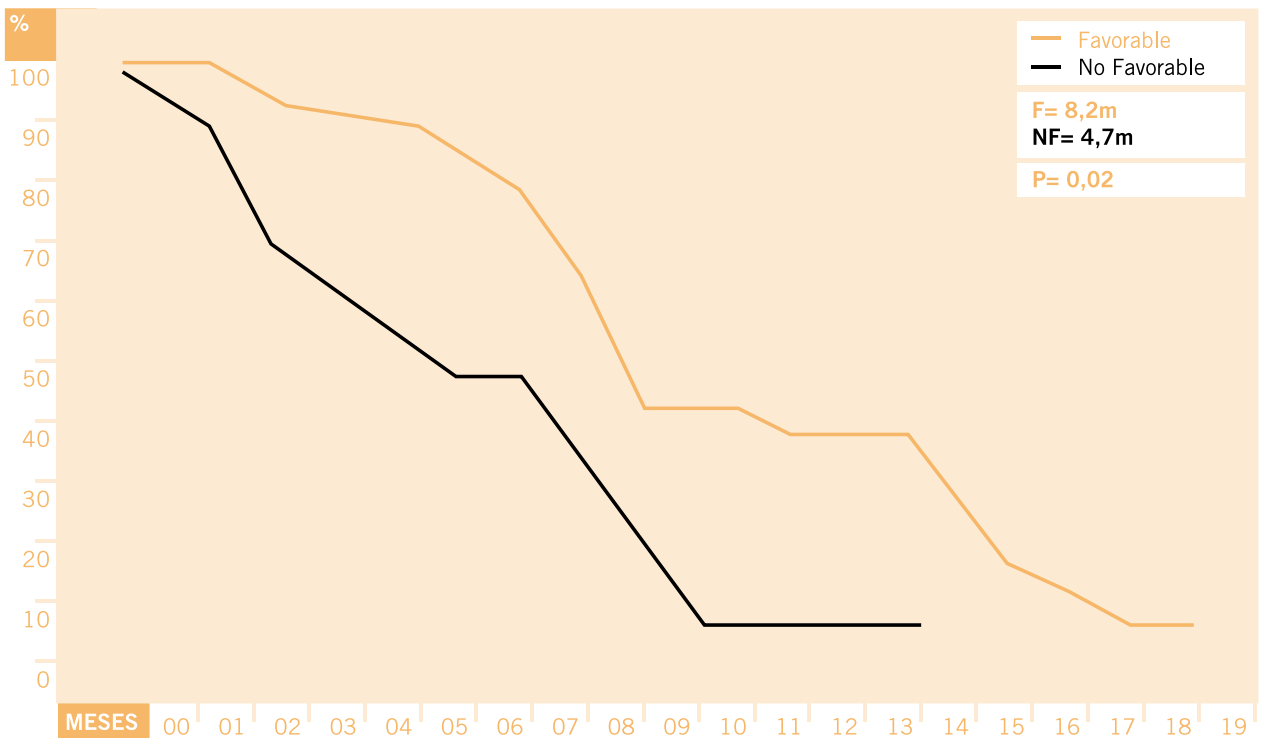


Figura 2: Tiempo a la progresión según polimorfismos genéticos (TS, XRCC1) en CCR tratado con 5-FU/OXA (39p)





muestra menos progresiones en el grupo de polimorfismos favorables, aunque sin llegar a presentar significación estadística.

Cuando se analizan las progresiones con respecto al polimorfismo de la TS únicamente, la diferencia alcanza la significación estadística (0-22%; $p=0,02$).

Cuando se analiza la toxicidad gastrointestinal grado III-IV, según el polimorfismo UGT1A1 en el subgrupo de 19 pacientes tratado con CPT-11+ 5-FU, no aparecen diferencias en cuanto a tener el polimorfismo favorable (6/6) y no tenerlo (X/7). Tampoco se observan diferencias en respuesta en el subgrupo de 39 pacientes tratados con 5FU+ OXA cuando se analiza según la combinación de los genes reparadores. No obstante cuando se analiza el tiempo a la progresión con la combinación de los 3 polimorfismos se obtiene diferencia con significación estadística en el grupo de pacientes con los polimorfismos favorables (9,2 m vs 6,8 m; $p=0,04$). (Figura 1). También mues-

tran diferencia significativa al tiempo a la progresión los polimorfismos de TS y XRCC1 en el subgrupo de pacientes tratados con 5FU+OXA (8,2 vs 4,7 meses; $p=0,02$) (fig 2). Los resultados no encuentran la relación esperada con la respuesta al tratamiento pero si muestran una clara diferencia significativa en el tiempo a la progresión lo que puede permitir la optimización del tratamiento a elegir en cada paciente.

El proyecto TTD está abierto e incluye a Junio de 2003, 7 ensayos clínicos cuyo estatus se muestra en la tabla 1. Los resultados del proyecto TTD se muestra en las tabla 2. Los primeros resultados corresponden a un ensayo fase II de tratamiento con 5FU/CPT-11 en pacientes mayores de 72 años y se mantiene la falta de significación en la RO cuando comparamos en 33 pacientes tratados en primera línea para enfermedad avanzada, el tener los polimorfismos favorables (TS 2/2) o no tenerlos (TS X/3). Asimismo tampoco existen diferencias al analizar la

Tabla 1: Estudio farmacogenómica Grupo TTD (junio 2003)

ESTUDIOS	PACIENTES INCLUIDOS	SUEROS ENVIADOS	I/E %
MOSAIC	294	141	48
02/TTD/01 (>72)	91	53	58
L-8005 (Triplet)	65	40	62
CPT.ES1.604 (TTDvsdeG)	169	97	57
02/TTD/00 (Oxa+UFT)	34	8	24
03/TTD/01 (Fase III Xeloda)	94	42	45
CPT.ES1-204 (pre-recto)	75	21	28

Tabla 2: Resultados preliminares 5FU + CPT11(TTD) >72 años

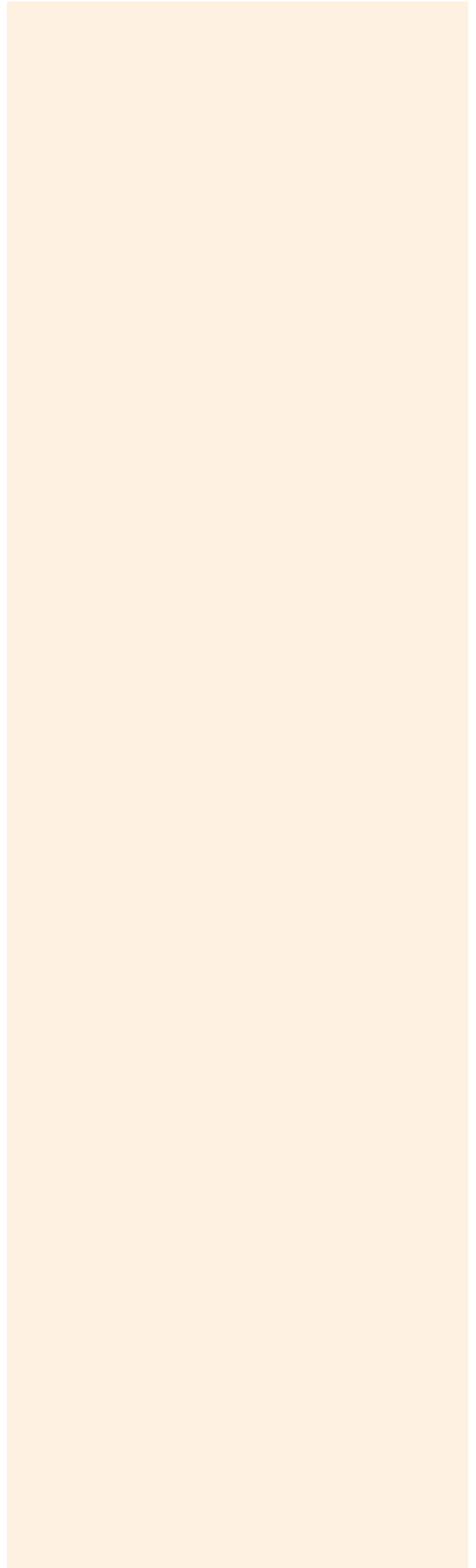
RESPUESTA 33p	TS 2/2 N(%)	TS x/3 N(%)
RO	3 (60)	10 (35)
EE	1 (20)	13 (46)
P	1 (20)	5 (17)



toxicidad gastrointestinal y neutropenia grado III-IV, en relación a tener el polimorfismo de la UGT1A1 favorable (6/6) o no tenerlo (X/7).

Los datos definitivos de este estudio y de un ensayo de triple combinación serán presentados en el Simposio.

NOTAS





Treatment of advanced colorectal cancer Irinotecan in combination treatment

Claus-Henning Köhne
Universitätsklinik Carl Gustav Carus,
Dresden. *Germany*

ABSTRACT

Irinotecan is considered standard treatment after failure with 5-FU/leucovorin(1;2). The different mechanisms of action and only partially overlapping toxicity profile were the rational to combine both compounds.

Phase I trials established several combination regimens(3-5). In Europe three infusional 5-FU regimens were developed that differed in there schedule (weekly or fortnightly) and whether 5-FU was modulated by leucovorin or not. In the USA a weekly bolus administration of 5-FU plus leucovorin was combined with the weekly administration of irinotecan. All but one regimen were tested in randomised clinical trials. All three comparisons revealed irinotecan in combination with 5-FU/LV to result in a significant higher response rate and longer median progression free survival or time to progression. Two studies also demonstrated a significantly prolonged median survival. Interestingly, the study with the highest response rate and longest progression free and overall survival failed to demonstrate a statistically significant difference in survival (Table 1). As more effective salvage treatment may have been effective in large enough number of patients to fail significance. However, it is estimated that about 80% of patients benefit from the upfront combination, as survival curves merge only after 28 months when 20% of patients were still alive.

In two trials (Table 2) combinations with irinotecan or oxaliplatin all combined with 5-FU/LV were compared in order to identify which compound would be more beneficial as a 1st line treatment. In the North American study the IFL regimen was compared to the FOLFOX4 regimen, while in the European trial FOLFIRI was



Table 1: Irinotecan, leucovorin, 5-Fluorouracil for 1st line treatment

REGIMEN	N PAT-ZAHL N	RESPONSE-RATE %	TTP MONTHS	SURVIVAL MONTHS
AIO- or LV5FU2	199	23	199	14,1
VS.	VS.	VS.	VS.	VS.
AIO/Irinotecan or LV5FU2/Irinotecan(6)	188	41 p=0,001	188 p=0,001	17,4 p=0,001
ILF-	231	39 p = 0,001	7,0 p = 0,004	14,8 p = 0,04
VS.	VS.	VS.	VS.	VS.
Mayo-/NCCTG-Regime	226	21	4,3	12,6
VS.	VS.	VS.	VS.	VS.
Irinotecan (7)	226	18	4,2	12,0
AIO (FU 2.6g/m ₂)	216	32	6.4	16,9
VS.	VS.	VS.	VS.	VS.
AIO (FU 2.0g/m ₂) / Irinotecan(8)	214	54 p < 0,001	8.5 p<.0001	20,1 p = 028

Table 2: Oxaliplatin or irinotecan-based combination with 5-Fluorouracil/leucovorin as 1st line treatment.

REGIMEN	N PAT-ZAHL N	RESPONSE-RATE %	TTP MONTHS	SURVIVAL MONTHS
ILF-Regime	264	29	6,9	14,1
VS.	VS.	VS.	VS.	VS.
FOLFOX	267	38 p=0,03	88 p=0,009	18,6 p=0,002
VS.	VS.	VS.	VS.	VS.
Irinotecan/Oxaliplatin (9)	264	28	6,7	16,5
1st LINE				
FOLFIRI	109	56	8,5	20,2
VS.	VS.	VS.	VS.	VS.
FOLFOX	111	54	8,1	21,5
"CROSS-OVER" AT PROGRESSION				
FOLFIRI	81	14	4,1	-
VS.	VS.	VS.	VS.	VS.
FOLFOX (10)	69	4	2,5	-



compared to FOLFOX. Thus, the American study utilised a 5-FU bolus regimen in the standard arm and an infusional regimen in the experimental arm. Further more, oxaliplatin based second line treatment after failure of IFL was only available in below 20% of patients because it was not registered and this not available to most patients in the US. In contrast, over 50% of patients who started with FOLFOX received irinotecan as a second line option. In the European trial both regimens contained infusional 5-FU and also a cross-over to the alternative regimen was predefined in the protocol and possible in over 60% of patients. This explains, at least in part, why the FOLOX was significantly more effective than the IFL regimen but was more or less equivalent to FOLFIRI in the European trial. Interestingly, in those trials, were infusional 5-FU plus irinotecan was followed by infusional 5-FU plus oxaliplatin or vice versa (Tournigand and EORTC 40986) the median survival time exceeded 20 months. Therefore, combination treatment should be the standard 1st line regimen and 5-FU monotherapy should be the exception.

5-FU prodrugs such as UFT and Capecitabine are orally administered and may be a substitution for infusional 5-FU(11;12). Combinations of these compounds with irinotecan gave promising results in phase II studies with response rates of about 50%. It appears logical to study these combinations relative to infusional 5-FU/LV. Large scale randomised trials are initiated. The three weekly administrations appeared more advantageous that the weekly administration of irinotecan when combined with capecitabine following the results of a randomised phase II study. Also,

capecitabine plus irinotecan or plus oxaliplatin had similar activity in a randomised phase II study(13).

Infusional 5-FU/LV is currently the preferred and best studied combination and should be considered as a standard 1st line regimen outside a clinical trial. The combination may also be combined with new agents of new targets such as the EGF receptor antagonist cetuximab or EGFr tyrosine kinase inhibitors(14). Early phase II studies using the IFL, AIO or LV5FU2 regimen gave promising results. In addition, VEGF(15) or COX-2 inhibitors are interesting drugs to be added to FOLFIRI regimens and their variants.

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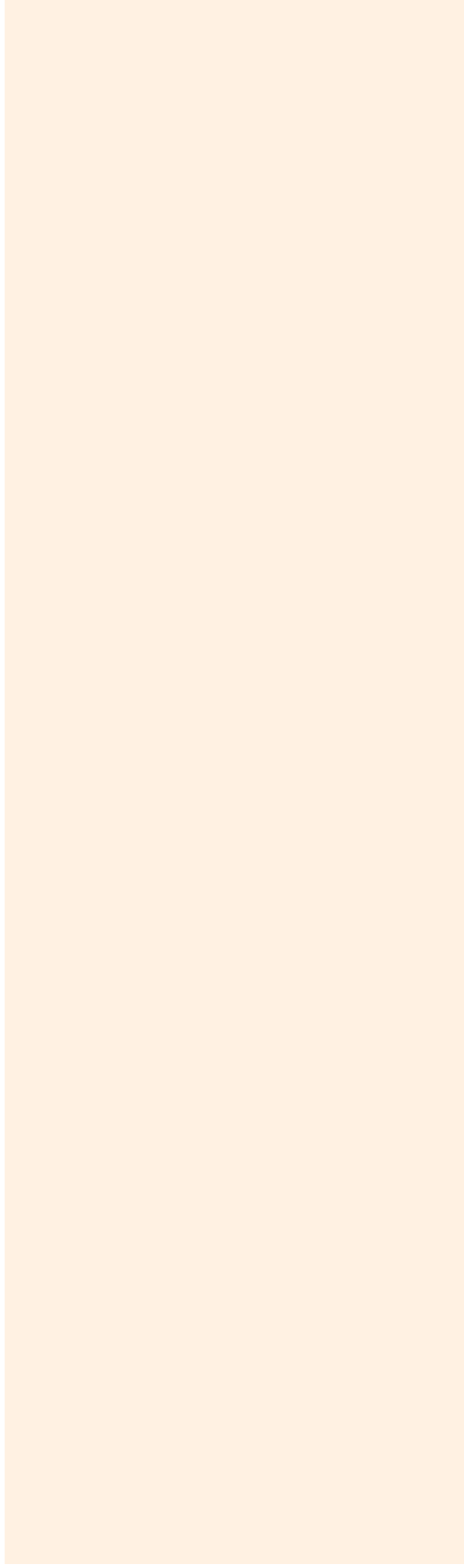


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NOTES





Oxaliplatin in combination chemotherapy for advanced colorectal cancer

Philippe Rougier

Hospital Ambroise Pare, Boulogne-Billancourt. **France**

ABSTRACT

Although 5-fluorouracil (5-FU) continues to be used in most of the regimens for treatment of advanced colorectal cancer (CRC), new drugs, combinations and schedules are still under investigation. Clinical practice has evolved from the use of 5-FU combined with folinic acid (FA) to 5-FU/FA combined with irinotecan (CPT-11) or oxaliplatin (LOHP) for the first and second line treatment of advanced CRC ; this has resulted into a doubling of the median survival time over that achieved with 5-FU alone. Ongoing researches try to further improve this situation with the development of multidisciplinary approaches (including surgery with hepatectomy, regional chemotherapy, and tumor destruction), by the biological characterisation of both tumours and patients by the use of molecular markers to better 'individualise' the treatment (tt) and the use of new products directed against new targets. Oxaliplatin plays an important role in these fields of investigation and will be specifically emphasized Oxaliplatin is a third-generation platinum compound (L-OHP;Eloxatin®) which has been approved for metastatic CRC in Europe in 1996 for first-line tt and for second line in France in 1996 and more recently in August 2002 in the US. Oxaliplatin in combination with fluorouracil:

The use of oxaliplatin in combination with 5-FU/FA is based on in-vitro synergy and the results of a phase III study conducted in 420 previously untreated patients that compared a combination oxaliplatin/5-FU/FA (FOLFOX 4) to the LV5FU2 regimen alone and demonstrated a benefit in terms of response rates (51% versus 22%; $P=0.0001$) and progression-free survival (PFS) [1] (9 vs 6 months; $P=0.0003$) in favor of [1] ; however the



improvement in overall survival (median: 16.2 vs 14.7 months) did not reach statistical significance ($P=0.12$) perhaps because patients were allowed to receive a second line tt. At the same period another phase III trial showed a high response rates (53%) when L-OHP was added to chronomodulated 5-FU/FA, but again with a non significant improvement in overall survival [2]. A third study using a weekly regimen of continuous 24h 5FU/HD folinic acid and Oxaliplatin (FUFOX) has been recently reported a significant increase in response rate (48.3% vs 22.6% ; $p<0.0001$) and PFS (7.9 vs 5.3 months ; $p<0.0001$) but not in the overall survival (20.4 vs 16.1 months ; NS), but patients had the possibility to receive a second and even a third line tt [3]. Other regimen combining L-OHP with 5-FU/FA has been reported [4] with favorable results. Recently the EGOG study [5, 6] comparing FOLFOX 4 (L-OHP/5-FU/FA) to a combination of CPT-11 and bolus 5-FU/FA (IFL) and a combination of L-OHP and CPT-11 (IRINOX) [5] has been reported. The toxicity profile of FOLFOX 4 was different and better than that of IFL whose toxicity seemed related to the bolus infusion of 5FU [5, 6] ; there was also an advantage for the FOLFOX regimen over the IFL regimen in term of RR (40% vs 30% ; $p=0.02$), TTP (8.8 vs 6.9 months ; $p=0.004$) and overall survival (19.1 vs 14.8 months $p=0.0006$) [5,6];. However in a comparison of the FOLFOX regimen to a combination of CPT-11 and infusional 5-FU/FA (FOLFIRI) an Italian study has reported equivalent results between FOLFIRI (using a 2 days continuous infusion of 5FU +, FA) and FOLFOX [7 colucci ASCO 2003, 1021] FOLFOX4 has also been investigated in second-line and reported it superiority over

oxaliplatin or LV5FU2 alone in term of RR (9.6% vs 1.1% vs 0.7% ; $p=0.05$) and TTP over LV5FU2 (4.6 vs 2.7 months ; $p=0.0001$) [8, 9].

Which sequence?: One important question is the choice of the first line tt for patients with advanced CRC and the best sequence of administration as first and second line tt between FOLFOX and FOLFIRI is still a matter of discussion. The comparison of the sequences FOLFIRI followed by FOLFOX or the sequence FOLFOX followed by FOLFIRI has been made and equivalent results with similar response rate (56 vs 53%), significant difference in TTP after the second lines of therapy (14.5 vs 11.9 months ; NS) and a similar overall survival (median 20.4 and 21.5 months) for each sequence respectively [10, 11]

High-dose (HD) intensity L-OHP has been investigated in second-line and suggested a high activity and an interesting progression free survival [12]. The recent results of the OPTIMOX trial at ASCO 2003 demonstrated that a HD regimen (130 mg/m² every 2 weeks) combined to a simplified LV5FU2 regimen for 6 cycles followed by LV5FU2 and reintroduction of L-OHP in case of progression was equivalent to the classical FOLFOX4 regimen in term of RR (63.1% vs 59.8%) PFS (9.2 vs 8.9 months) and superior in term of tolerance (grade 3-4 neutropenia: 21% vs 32%; $p=0.009$; grade 3 neuropathy: 11% vs 19%; $p=0.0017$) [12].

Hepatic arterial infusion of L-OHP is also being investigated [13] and resulted in a high response rate combined with iv 5FU/FA and is investigated in combination with more active systemic chemotherapy.

In all these trials peripheral sensory neuropathy has been the cumulative dose-



limiting toxicity and some attempts to decrease this toxicity are in progress. Oxaliplatin combined to irinotecan. As L-OHP and CPT-11 act synergistically [14, 15], and because their toxicity profiles are non-overlapping they have been combined in metastatic CRC. A phase III comparing CPT-11/L-OHP vs CPT-11/5-FU/FA reported an acceptable toxicity for the CPT-11/L-OHP combination [16]. The combination of CPT-11 and L-OHP has also been investigated in second-line with an overall response rates of 49% and 29% in two phase II studies conducted in 5-FU resistant metastatic CRC [17, 18], but this response rate has not been confirmed in a randomised phase II trial of FOLFIRI, FOLFOX and CPT-11/L-OHP (11.4% vs 21.2% vs 15%, NS) even if there was a good overall survival [19]. Triple therapy and regimens containing 5-FU/FA/CPT-11/L-OHP are also safe and active both first- [20, 21] and second- [22, 23] line with a high response rate (60 to 70%).

Raltitrexed. Raltitrexed has been combined with L-OHP in first-line with a RR ranging from 41.5% to 54% [24, 25] but with a risk of severe toxicity (febrile neutropenia...) in patients with renal insufficiency.

Oral fluoropyrimidines. Oral fluoropyrimidines have over iv bolus 5FU/FA an added benefit of ease of administration with a patient preference and a better tolerance. Capecitabine significantly improved the response rate (26% versus 17%, $P < 0.0002$) and the 5-FU prodrug tegafur combined with uracil referred as UFT reported a response rate and overall survival equivalent to bolus 5FU/FA with a better tolerance.

The combinations of capecitabine or UFT with L-OHP are under exploration. and a response rate of around 50% and a tolerable safety profile has been reported [26-28]. An interim analysis of a randomised phase II comparison of capecitabine with either CPT-11 or L-OHP indicates that the two regimens have similar activity with response rates of 38% and 42% for the CPT-11 and L-OHP containing arms, respectively [29].

New drugs. The antibody C225, anti-epidermal growth factor receptor (EGFR) (cetuximab; Erbitux™) is active alone [30], or in combination with CPT-11 [31] towards CPT-11 refractory CRCs that express EGFR. Results of the ongoing two-arm BOND trial comparing cetuximab vs cetuximab /CPT-11 in pts who have progressed on prior CPT-11 therapy demonstrated an advantage of the combination in terms of TTP. Cetuximab is presently tested in combination with LOHP with encouraging results. The anti-VEGF antibody bevacizumab which is efficient in combination with 5-FU/FA or CPT-11/5-FU/FA is also tested in combination to LOHP. In the future an increasing number of anti-tumour agents targeting specific molecular changes involved in the development of CRC will be tested.

Chemotherapy using oxaliplatin and liver resection. Only 10-20% of patients have hepatic metastases suitable for resection, and approximately 70% of patients will experience intrahepatic recurrence, despite improvements in resection techniques, and the use of cryosurgery and radiofrequency ablation. The combination of L-OHP with 5-FU/FA regimens has been used for these patients with interesting results especially in preoperative where a reduction of the



tumor size by >50% in 59% of a subset of 151/389 pts with one metastatic site has been reported and facilitated the resection of liver metastases in 77/389 (19%) pts with previously unresectable metastases [32]. Presently an EORTC intergroup trial is evaluating the interest of a pre and postoperative chemotherapy using FOLFOX4 in pts with resectable liver metastases compared to surgery alone (250 patients included) and will answer this important question.

Is patient selection a way forward? Recently molecular studies have demonstrated that biological characteristics of tumours may influence the efficacy of and tolerance to chemotherapy. There is increasing evidence that patient selection could significantly impact on treatment outcomes.

Predicting chemotherapy response and toxicity. Molecular makers of CRC for response to chemotherapy are likely to be used alongside clinical prognostic indicators. However if it is quite well established for 5FU [33, 34]. For L-OHP potential markers of response are enzymes involved in DNA damage repair. Resistance to L-OHP may be explained by an increased in DNA repair and tumors with low DNA repair enzymes or with gene polymorphisms may be more sensitive to L-OHP. Among genetic polymorphisms tested XPD Lys751Lys, ERCC-1 and GSTP1 polymorphisms were independent predictors of response to L-OHP/5-FU [35-39]. Identification of the molecular determinants of toxicity is also important in planning chemotherapy for CRC patients because minimising toxicity will improve both patient survival and quality of life, however there is biological predictive factor for L-OHP toxicity,

especially for the neurotoxicity which remains its main limiting toxicity.

CONCLUSIONS

L-OHP plays a leading role in the management of patients with CRC and may still have, with CPT-11, a central role in the future management of advanced CRC with the development of oral fluoropyrimidines, and the apparition of new agents, biologically-targeted against EGF and VEGF receptors. The CRC patient management decisions will depend more and more on our knowledge of prognostic and predictive markers for chemotherapy sensitivity and toxicity.

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The role of the combination of oxaliplatin, irinotecan and 5-FU in advanced colorectal cancer.

Eric Van Cutsem

University Hospital Gasthuisberg,
Leuven. *Belgium*

ABSTRACT

The prognosis of patients with metastatic colorectal cancer has improved over the last years. It has clearly been shown that irinotecan and oxaliplatin contribute to the improved outcome. Indeed many studies demonstrate that the more patients are exposed to as well the fluoropyrimidines, as irinotecan, as oxaliplatin, the longer the median survival is. The median survival approaches 20 months in recent studies in which >60–70 % of patients are exposed to all 3 drugs. In all these studies the patients were treated by a first line treatment of 5-FU/FA/irinotecan or 5FU/FA/oxaliplatin and later after progression patients were treated with resp 5-FU/FA/oxaliplatin and irinotecan or 5-FU/FA/irinotecan.

Important strategic questions arise on the combined use or sequential use of the cytotoxic agents. There is ample evidence to state that the majority of patients benefit from an upfront combination of 5-FU/FA/oxaliplatin or 5-FU/FA/irinotecan. However there are actually no clear reasons to combine the fluoropyrimidines, irinotecan and oxaliplatin in the first line treatment of metastatic colorectal cancer. Until now relatively few phase 1 and phase 2 studies have been reported. They show that the simultaneous combination of 5-FU, irinotecan and oxaliplatin are more toxic and suggest that it is unlikely that an upfront 3 drug combination can further improve the outcome of patients with metastatic colorectal cancer.

A specific situation where the 3 drug combination should certainly be investigated is the neoadjuvant treatment of unresectable liver metastases with the aim to try to induce an important regression in order to make a resection of the liver metastases possible. More pros-



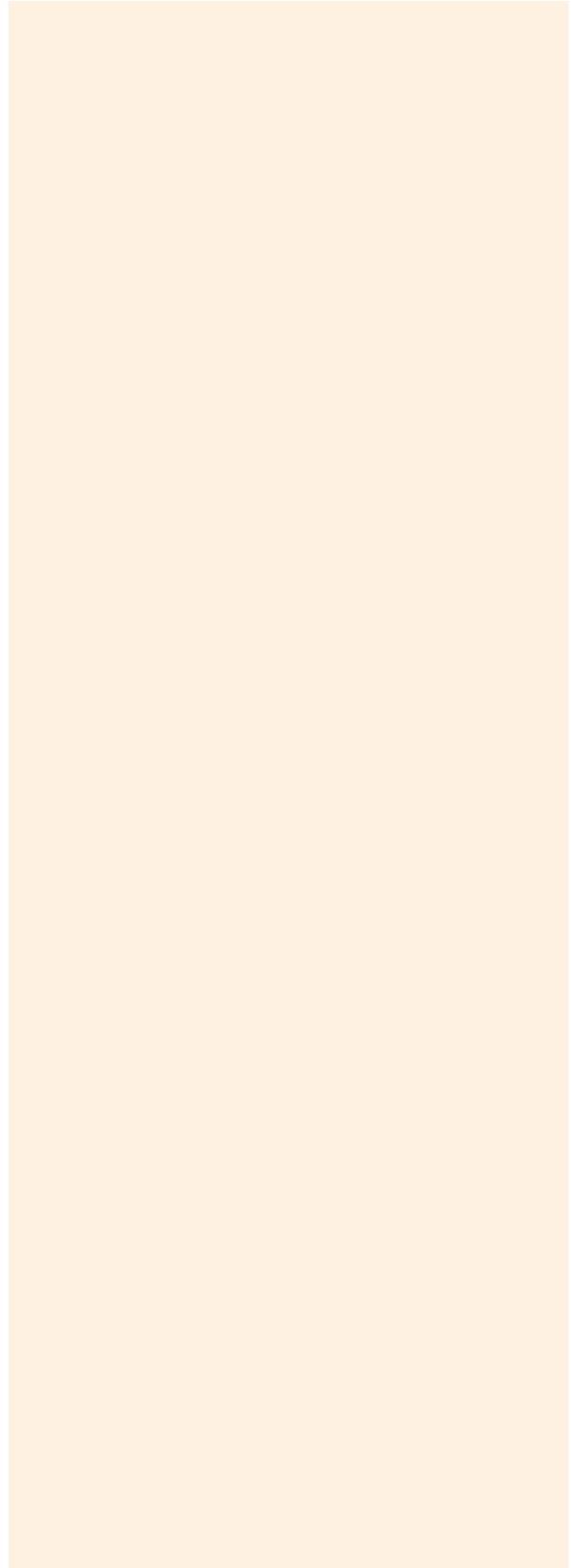
pective data are needed in this setting. Moreover the development of the novel targeted agents (EGFR and VEGF inhibitors) in combination with cytotoxic treatment make the concomitant use of the 3 cytotoxic agents very unlikely in the majority of patients.

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¿Capecitabina o infusión continua de 5-FU?

Bartomeu Massutí

*Hospital General Universitario,
Alicante. España*

5-FLUOROURACILO

El 5-fluorouracilo (5FU) es un antimetabolito introducido en la clínica en 1957, fue diseñado tras la observación de que las células neoplásicas utilizan uracilo con mayor intensidad que las células no transformadas y ha venido constituyendo el fármaco central en el tratamiento del Cáncer Colorrectal (CCR) hasta la actualidad y se ha utilizado extensamente en el tratamiento de la enfermedad avanzada y en el tratamiento adyuvante postquirúrgico (1,2). Se ha realizado una investigación continuada para la optimización de su uso que ha sido paralela al aumento de los conocimientos en sus mecanismos de actuación bioquímica (3). El 5FU es un profármaco y en sus vías metabólicas de activación/degradación se forman 3 compuestos claves en su acción citotóxica: el 5FdUMP que inhibe el enzima Timidilato-Sintetasa (TS) que constituye un enzima limitante en la síntesis del ADN; el 5-FUTP que se incorpora al ARN de forma alterada y el 5-FdUTP que se incorpora al ADN en lugar del dTTP que constituye el sustrato normal de la ADN-polimerasa. El 5FU se caracteriza por una muy corta vida media una vez administrado de forma intravenosa (4). Inicialmente la respuesta objetiva tras su administración en bolus alcanzaba solamente el 10% y posteriormente se desarrollaron los mecanismos de modulación bioquímica mediante ácido folínico, methotrexate o interferones que lograron incrementar las tasas de respuesta hasta casi duplicarlas aunque sin claro impacto en la supervivencia (5,6,7).

INFUSIÓN CONTINUA DE 5FU

Las consideraciones teóricas que se derivan de la farmacocinética, farmacodinámica y efectos citotóxicos del 5FU han determinado la investigación de su administración mediante infusiones intravenosas



prolongadas (infusión continua – i.c.). El objetivo de dichas administraciones es permitir una exposición constante de las células neoplásicas al fármaco a lo largo del ciclo de división celular asegurando su interacción durante la fase S del ciclo. Se han desarrollado múltiples esquemas de administración para la i.c. de 5FU desde 24 horas hasta 42 días. La administración del 5FU en i.c. determina el predominio de la citotoxicidad mediada por la inhibición de la TS y permite incrementar la dosis total administrada de 5FU; al mismo tiempo se observa un cambio en el patrón de efectos secundarios/toxicidades limitantes con reducción de mielosupresión y mucositis e incremento de diarrea y síndrome mano-pie. Entre los esquemas de i.c. que permiten administrar la máxima intensidad de dosis figura la administración en infusión continua de 48 horas con periodicidad semanal de hasta 3500 mg/m²/semana (esquema TTD) (8). En los análisis retrospectivos de los esquemas con 5FU existe una relación dosis-toxicidad-esquema de administración y aparece una tendencia para una relación dosis-respuesta-supervivencia (9). La adición de la modulación bioquímica a la i.c. ha resultado en la reducción de dosis total de 5FU administrada (10). Un metanálisis de estudios comparativos entre 5FU bolus o i.c. en CCR evidencia un beneficio para la i.c. con superioridad para tasa de respuesta (22 vs 14%), supervivencia (HR para i.c. 0.88) y reducción de toxicidad hematológica G3-4 (34 vs 13%) (11).

TRATAMIENTO QUIMIOTERÁPICO DE COMBINACIÓN EN CCR

Con la introducción de nuevos fármacos activos en CCR (Irinotecan, Oxaliplatino) se ha establecido la superioridad de los esquemas de combinación de dos fármacos (5FU+CPT-11 o 5FU + Oxaliplatino)

respecto a la utilización de agentes únicos en el tratamiento de primera línea del CCR avanzado (12,13). En los esquemas de combinación, la i.c. 5FU muestra una superioridad en su perfil de toxicidad respecto a la administración en bolus (14,15). En estas combinaciones la modalidad de i.c. de 5FU ha sido la de 24-48 h en administración semanal o quincenal.

LIMITACIONES DE LA I.C.

Los esquemas de administración de 5FU en i.c. requieren la colocación y mantenimiento de accesos venosos centrales y la utilización de dispositivos de infusión. Asimismo, los esquemas de administración determinan unos requerimientos elevados de frecuentación hospitalaria y de cuidados médicos y de enfermería. Los riesgos de complicaciones infecciosas o vasculares asociadas a los dispositivos vasculares son limitados pero precisan de entrenamiento y protocolos específicos de uso y mantenimiento (16). Inicialmente los costes asociados a la administración de la i.c. se ven incrementados pero existen potenciales alternativas organizativas que pueden permitir controlar los costes e incrementar la satisfacción y calidad de vida (CDV) de los pacientes (17).

PREFERENCIAS ENTRE TRATAMIENTO

Estudios comparativos con diseño prospectivo y metodología validada ponen de manifiesto que las preferencias de los pacientes favorecen la vía oral para la administración de tratamientos quimioterápicos. Esta preferencia alcanzaba el 89% y se basaba en razones de comodidad, permanencia en su domicilio, reducción del desplazamiento a centros hospitalarios e inconvenientes causados por la



manipulación e infusión intravenosa, aunque el 70% de los pacientes no aceptaban perder eficacia en razón de su preferencia inicial (18). En una comparación cruzada entre 5FU i.v. y Tegafur-uracilo oral, el 84% de los pacientes mostró preferencia para el tratamiento con fluoropirimidinas orales y el orden de secuenciación de los tratamientos no influyó en las preferencias de los pacientes (19). A pesar de ello, persisten problemas potenciales en el cumplimiento del tratamiento oral, posible pérdida de eficacia por dificultades en interindividuales en la absorción y reducción del control médico; asimismo se precisan análisis farmacoeconómicos amplios para evaluar el impacto en los costes.

FLUOROPIRIMIDINAS ORALES

El 5FU es un profármaco que precisa pasar al interior de la célula y su metabolismo enzimático para su efecto citotóxico. Su biodisponibilidad oral es escasa y ampliamente variable por lo que se han venido investigando y desarrollando otras pirimidinas fluoradas con perfil farmacológico más favorable que permitieran su administración oral. Entre estos fármacos se encuentran: Tegafur (Tetrahydrofuril-5FU), Doxifluridina (5-dFUR), UFT (Tegafur-Uracilo 1:4), Capecitabina (generación diferenciada de 5FU mediada por Timidin-Fosforilasa), S-1 (asocia Tegafur con 5-cloro-2,4-dihidroxipiridina inhibidor de DPD y con oxonato potásico) y Etiniluracilo (administrado 10:1, inactiva DPD) (20). Estos fármacos presentan un diferente grado de desarrollo y su comparación directa con 5FU i.v. ha sido infrecuente.

UFT

El conocimiento del metabolismo de las fluoropirimidinas ha puesto de manifiesto el papel decisivo del enzima Dihidro-piri-

din-deshidrogenasa (DPD) como enzima limitante y regulador del anabolismo del 5FU. DPD es determinante en la variabilidad interindividual observada en el 5FU. En la línea de inhibición de DPD para modular el metabolismo del 5FU se ha desarrollado el UFT (Tegafur-Uracilo en proporción molar 1:4) que limita el catabolismo del 5FU, reduciendo algunas de sus toxicidades y permite asimismo su asociación a la modulación bioquímica mediante ácido fólico (AF) (21). En 2 EC comparativos de UFT frente a 5FU en bolus con modulación mediante AF se comprueba equivalencia en supervivencia y respuesta pero con un menor tiempo a la progresión para el grupo tratado con fármacos orales (22,23).

CAPECITABINA

Es un carbamato de fluoropirimidina diseñado para ser resistente a DPD y que mediante un metabolismo de tres pasos enzimáticos (CE, Citidin-desaminasa, y Timidin-Fosforilasa) libera 5FU de forma selectivamente incrementada en las células neoplásicas (24). Se absorbe en el intestino sin metabolizarse al resistir la acción de la pirimidin-nucleósido-fosforilasa intestinal. La TP que determina la liberación final de 5FU es un factor angiogénico asociado a neoplasias y su actividad está incrementada en las células neoplásicas lo que determina que en modelos animales experimentales las concentraciones de 5FU se incrementen hasta 127x en el tejido tumoral respecto de los niveles en plasma o tejidos normales (25). En modelos experimentales Capecitabina muestra una eficacia superior a la del 5FU y a 5-DFUR, su actividad se potencia mediante modulación con AF y es eficaz en tumores resistentes a 5FU. En los EC Fase I con diferentes esquemas de administración la diarrea



fue la toxicidad limitante de dosis. Posteriormente se llevó a cabo en pacientes con CCR un EC Fase II comparativo entre la administración continua, la administración intermitente y la modulación con AF sin evidenciarse diferencias en respuesta ni supervivencia pero con mejor tiempo a la progresión (7.7 m) en el esquema de administración intermitente (1250 mg/m²/12 h d1-14 cada 21 d) (26). Finalmente EC Fase III frente a 5FU bolus modulado con AF han evidenciado superioridad para Capecitabina en términos de tasa de respuesta (25.7 vs 16.7%) con equivalencia en tiempo a la progresión y supervivencia (27,28). En lo referente al perfil de efectos secundarios los pacientes tratados con Capecitabina mostraron una menor incidencia de neutropenia, mucositis, diarrea, náuseas y alopecia y un menor número de pacientes precisaron ajuste/reducción de dosis.

El diseño y mecanismo teórico de acción de la Capecitabina podría ser equivalente a la administración de 5FU en i.c. pero los EC prospectivos que pueden definir/confirmar esta hipótesis están en desarrollo y se realizan en esquemas de combinación con CPT-11 u Oxaliplatino.

CAPECITABINA EN COMBINACIÓN

Se han definido de forma acelerada mediante EC Fase I-II las combinaciones de Capecitabina con CPT-11 y Oxaliplatino. Aunque existe una diversidad de esquemas, globalmente la dosis de Capecitabina de 1000 mg/m²/12h d1-14 cada 21 días puede asociarse a las dosis habituales de Oxaliplatino y CPT-11 usadas en combinación y las tasas de respuesta con dichas combinaciones superan el 50% (29-32).

CAPECITABINA Y RADIOTERAPIA

El 5FU en i.c. ha mostrado su potencial radiosensibilizante cuando se administra de forma concurrente con radioterapia en el Cáncer Rectal tanto en el contexto pre como post-operatorio. También Capecitabina ha iniciado su desarrollo en asociación a Radioterapia en esta área y los estudios Fase I disponibles permiten recomendar la dosis continuada de 825 mg/m²/12 h como agente único (33) o la dosis 825 mg/m²/12 h d1-14 y d22-35 cuando se administra conjuntamente con Oxaliplatino a dosis de 50 mg/m²/semana con remisión completa patológica del 19% y cirugía completa en 79% (34).

PERSPECTIVAS

_Los antimetabolitos pirimidínicos continúan constituyendo el eje del tratamiento quimioterápico del CCR desde sus estadios iniciales hasta los avanzados.

_En los esquemas de combinación la i.c. de 5FU ofrece un mejor perfil de efectos secundarios y permite la asociación a dosis plenas con CPT-11 u Oxaliplatino.

_La i.c. de 5FU presenta una cierta complejidad para los pacientes y requiere experiencia organizativa.

_El desarrollo de fármacos fluoropirimidínicos orales ha confirmado su equivalencia a 5FU administrado en bolus

_La administración oral de fármacos es preferible desde el punto de vista de los pacientes

_Los fármacos orales se han integrado en los esquemas actuales de combinación manteniendo tasas de eficacia comparables a los esquemas que asocian 5FU en i.c.

_Entre los fármacos orales, la Capecitabina ofrece un perfil de acción que podría resultar equivalente a la i.c. de 5FU.

_La Capecitabina se puede administrar de forma concomitante con radioterapia en el tratamiento preoperatorio del Cáncer de Recto.



_En los esquemas de combinación la superioridad de respuesta que alcanza el 5FU en i.c. podría ser menos determinante.

_Se están desarrollando EC de esquemas de combinación que evalúan de forma comparativa la administración de 5FU i.c. o Capecitabina que resultarán determinantes en la evolución de los tratamientos quimioterápicos del CCR (EC 03-TTD-01)

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NOTAS





¿Cómo tratar a los pacientes ancianos con cáncer colorrectal?

Javier Sastre

Hospital Universitario Clínico San Carlos, Madrid. *España*

RESUMEN

La longevidad creciente en los países desarrollados, y la alta frecuencia de determinados tumores en el anciano, han despertado en los últimos años un especial interés por el estudio del comportamiento del cáncer en dicha población. El cáncer de colorrectal (CCR) es una enfermedad que se presenta mayoritariamente en la sexta-séptima décadas de la vida. Dada la avanzada edad de muchos de los pacientes con CCR, en numerosas ocasiones son excluidos de actitudes quirúrgicas agresivas, de tratamientos con quimioterapia o radioterapia adyuvantes, y de tratamiento con quimioterapia en la enfermedad metastásica, que comportan altos riesgos de toxicidad y morbimortalidad. De hecho, esta "discriminación en razón de la edad" se manifiesta en la baja representación de este subgrupo de pacientes en los ensayos clínicos (alrededor del 20%), lo que hace difícil extrapolar los resultados tanto de actividad como de toxicidad a dicha población. Esto refleja la necesidad de nuevos estudios diseñados para la población anciana, que permitan extraer conclusiones fiables acerca de la conducta a seguir en dicha población.

Ciertamente, los pacientes ancianos presentan con mayor frecuencia problemas de salud y socioeconómicos que pueden condicionar su tratamiento, pero no es menos cierto que el uso de escalas específicas de evaluación de la comorbilidad y del estado funcional del anciano (Cumulative Illness Rating Scale-Geriatric ó Charlson Scale), así como el conocimiento de las alteraciones de aclaramiento renal, flujo hepático, capacidad de detoxificación y reserva medular del anciano nos pueden permitir una mejor selección, reduciendo el porcentaje de pacientes excluidos de un tratamiento potencialmente beneficioso (1).



Ante un paciente anciano con carcinoma colorrectal avanzado irreseccable, es preciso, más aún si cabe que en el paciente joven, la individualización de la decisión terapéutica, en base a diferentes parámetros:

Estado general del paciente: es probablemente el principal factor condicionante tanto de la respuesta terapéutica como de la tolerancia a la quimioterapia. Antes de decidir un programa cistostático específico en un paciente anciano es preciso una evaluación muy estricta, con atención especial a aquellos aspectos de la historia clínica del paciente que nos puedan alertar sobre la posibilidad de que se trate de un "anciano delicado". Aunque existen varias definiciones de "anciano delicado", el concepto general es el de un "paciente de edad avanzada, dependiente para las actividades de la vida cotidiana, con mínimas reservas funcionales orgánicas, y sin posibilidad para mejorarlas". Vinograd y cols (2), llevan este concepto a la práctica clínica mediante la evaluación de una serie de parámetros como son:

1. Edad igual o superior a los 85 años
2. Dependencia para una o más de las actividades cotidianas.
3. Presencia de tres o más enfermedades concomitantes, enfermedades cardiorrespiratorias o cerebrovasculares importantes ó evaluación a través de escalas específicas de patologías asociadas (Concomitant Illness Rating Scale, Charlson Scale).
4. Presencia de uno o más síndromes geriátricos:

_Demencia moderada-severa (Folstein minimal status de 25 o menor)

_Tres o más caídas al mes.

_Delirio en presencia de infección urinaria o respiratoria, angina o fármacos.

_Incontinencia urinaria en ausencia de estrés, infección, diuréticos o hiperplasia prostática.

_Incontinencia fecal en ausencia de diarrea o laxantes.

_Fracturas osteoporóticas de huesos largos o aplastamientos vertebrales.

_Situación de abandono o malos tratos.

_Imposibilidad para mejorar con medidas farmacológicas o de rehabilitación.

Potencial rescate quirúrgico postquimioterapia: La curación de un paciente con cáncer colorrectal avanzado inicialmente irreseccable es hoy día una realidad con el desarrollo de regímenes de poliquimioterapia con fármacos nuevos (irinotecán, oxaliplatino) (3). Pacientes ancianos seleccionados podrían beneficiarse de un manejo agresivo de intención curativa.

Patología concomitante en el anciano: los pacientes con enfermedad coronaria severa son malos candidatos al tratamiento con 5FU, especialmente en regímenes de infusión continua. Además, los pacientes con Diabetes Mellitus, HTA, EPOC y otras enfermedades crónicas, pueden sufrir descompensaciones secundarias a diarreas severas, neutropenias febriles o emesis graves, relativamente frecuentes con el uso de la poliquimioterapia.

Toxicidad de la quimioterapia: en un análisis preliminar de un estudio fase II con 76 pacientes ancianos con CCR avanzado y ECOG menor o igual a 2 (con una media de edad de 76 años), que fueron tratados con tomudex 3 mg/m² cada 21 días, se vio que la toxicidad moderada-severa no era mayor del 11,6% (las más frecuentes eran diarrea, astenia, náuseas y vómitos, toxicidad hepática)(4). La introducción de fluoropirimidinas orales ha supuesto un nuevo tratamiento activo con un perfil tóxico favorable y además preferido por los pacientes con el objeto de reducir la frecuentación hospitalaria (5,6,7)



Nivel sociocultural y apoyo familiar del anciano: aunque en general, los regímenes de monoquimioterapia con fluoropirimidinas orales aportan mejor tolerancia y menor dependencia hospitalaria, los ancianos con bajo nivel sociocultural y escaso apoyo familiar pueden mal interpretar las prescripciones médicas e incurrir en situaciones de infra o sobredosificación, con todos los problemas derivados de ello. Además, estos pacientes reciben otras medicaciones por patología concomitante con los consiguientes riesgos de error en la toma de citostáticos orales.

ESTUDIOS DE QUIMIOTERAPIA ESPECÍFICOS EN LA POBLACIÓN ANCIANA

La **Tabla 1** recoge los estudios realizados en pacientes ancianos hasta la actualidad. Como se puede observar, los estudios son recientes y muy escasos, especialmente si comparamos con el número anual de estudios publicados en cáncer colorrectal avanzado en población no anciana, la mitad de ellos retrospectivos, con un número no muy elevado de pacientes y empleando monoquimioterapia con fluoropirimidinas orales, 5-FU o tomudex (8,9,10,11,12,13). Todos estos regímenes se han mostrado tolerables por la población anciana con buen estado general, con toxicidad grado 3/4 del NCI-CTC por debajo del 10%, con excepción de la diarrea que provocan algunos regímenes de 5-FU + LV como el de la Clínica Mayo. No obstante, la actividad antitumoral mostrada (RO 13-29%), aunque similar a la observada con estos mismos regímenes en la población no anciana, es inferior a la que se obtiene con los esquemas de combinación.

La poli-quimioterapia no ha sido ensayada de forma prospectiva en la población

anciana hasta fechas muy recientes. Por ello, el Grupo Español para el Tratamiento de los Tumores Digestivos (TTD) ha llevado a cabo un estudio prospectivo, multi-institucional, en pacientes >72 años, con la combinación de CPT-11 180 mg/m² + 5-FU 3 g/m² ic 48h de forma quincenal, como primera línea de tratamiento de la enfermedad avanzada. Se han seleccionado pacientes con buen estado general (IK 70-100), sin enfermedad coronaria, con recuentos hematológicos normales, niveles basales de bilirrubina <del LSN y aclaramiento de creatinina >60 ml/min. Se excluyeron pacientes con trastornos neurológicos o psiquiátricos importantes o síndromes geriátricos que definen al "anciano delicado". Entre Julio 2001 y Noviembre 2002 se han tratado 91 pacientes con dichas características. Un análisis preliminar sobre 83 pacientes muestra una buena tolerancia al tratamiento, siendo la neutropenia asintomática el efecto adverso grado _ mas frecuente (18%), seguido de diarrea 14%, astenia 9.6% y dolor cólico abdominal 7%. Se produjo tan solo 1 caso de fiebre neutropénica no complicada y aparecieron 5 eventos vasculares tromboembólicos. Hubo 2 muertes tóxicas secundarias a diarrea G-4 e insuficiencia renal en un caso y hemorragia gastrointestinal severa en el otro. Se obtuvo respuesta objetiva en el 34,6% de los pacientes y la enfermedad progresó precozmente en tan solo el 16%. La mediana de tiempo a la progresión es de 7.4 meses, por encima de la publicada en los estudios fase III de pacientes no ancianos con cáncer colorrectal avanzado (14).

Un análisis de factores pronósticos en los pacientes tratados con la rama CPT-11 + FU/LV del estudio V-303 publicado por Douillard y cols (Lancet) presentado por



Rougier y cols demuestra que la edad > 65 años no constituye un factor pronóstico adverso ni para toxicidad, ni respuestas ni supervivencia global, excepto un ligero incremento en la proporción de neutropenia febril (15). También un grupo de Milán ha presentado la asociación CAPIRI en pacientes ancianos con Xeloda en régimen clásico mas CPT-11 semanal 60 mg/m² días 1,8 y 15, ambos cada 4 semanas. La tasa de RO fue del 32% con un perfil tóxico muy favorable (16). Otro grupo italiano ha evaluado la asociación FOLFOX con 100 mg/m² de oxaliplatino repartido en 2 dosis, y nuevamente se obtuvo una tasa de RO del 32% con buena tolerancia (17). Estos estudios vienen a poner de relieve el papel de la poliquimioterapia en los pacientes ancianos “no delicados”, siendo preciso en el futuro comprobar si en esta población, al igual que en los pacientes jóvenes, el incremento de actividad de la poliquimioterapia se traduce en un incremento de supervivencia.

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Tabla 1: Estudios en ancianos con cáncer colorectal.

AUTOR	FECHA	ESTUDIO	EDAD	Nº PTS	TRATAMIENTO
FALCONE	1994	Prosp.	>70	43	Doxofluridina
FELIU	1997	Prosp.	>70	38	UFT-LV
CHIARA	1998	Retrosp.	>65	82	5FU-LV
POPESCU	1999	Retrosp.	>70	186	5FU · 5FU+LV o IFN 5FU-MMC · Tomudex
G.PAREDES	1999	Prosp.	>70	116	Tomudex
ABAD	2000	Prosp.	>72	214	UFT+/-LV
MAGNÉ	2002	Retrosp.	>70	86	5FU+LV

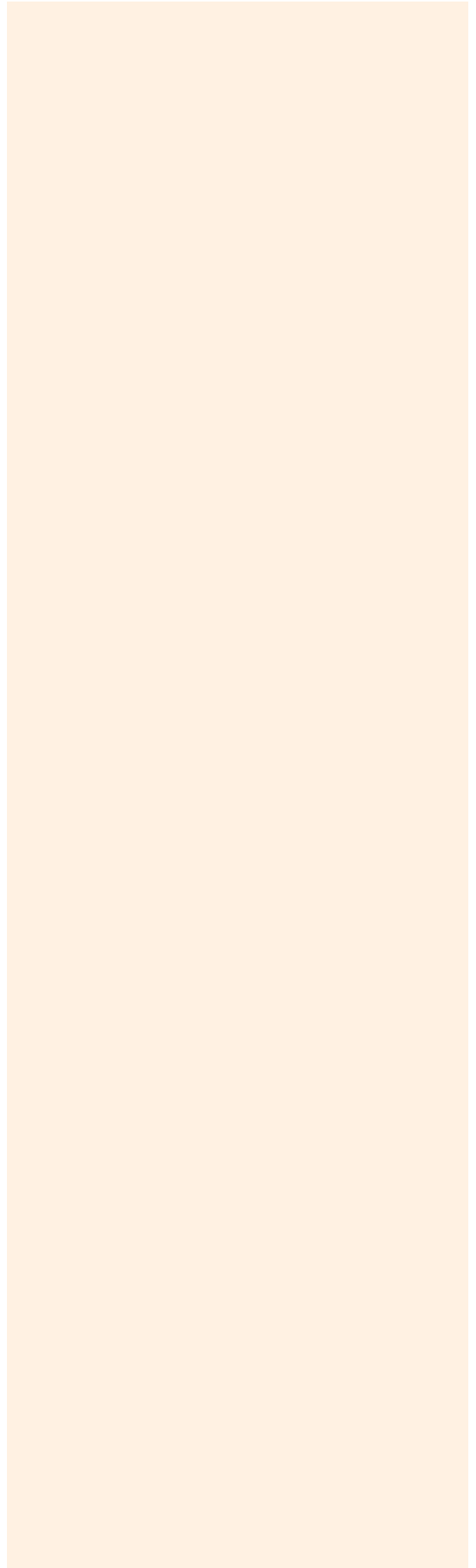


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NOTAS





Cáncer de colon avanzado. Experiencia del Grupo TTD

Enrique Aranda

Hospital Universitario Reina Sofía,
Córdoba. *España*

RESUMEN

El cáncer colorrectal ocupa el tercer lugar en frecuencia en el hombre y el segundo en la mujer. Es la cuarta causa de mortalidad por cáncer en los países occidentales por lo que representa un importante problema de salud pública. Si tenemos en cuenta que más del 50% de los pacientes con cáncer colorrectal tendrán enfermedad metastásica o localmente avanzada irresecable en algún momento de la evolución de la enfermedad, el tratamiento sistémico adquiere un importante papel en la estrategia terapéutica de ésta neoplasia.

Tras el empleo de múltiples fármacos y combinaciones el 5-Fluorouracilo se situó en la década de los 70 como el fármaco más activo, y hoy día, tras haber potenciado su eficacia con la modulación bioquímica y con la infusión continua, sigue siendo en combinación, el citostático de elección en primera línea de tratamiento. Ya no es discutible el beneficio de la quimioterapia en el cáncer de colon metastático o avanzado. El dilema actual estriba en decidir cuál es el mejor tratamiento quimioterápico que puede recibir un paciente en base a las características que presenta, ya sea inherente a la neoplasia o al propio paciente.

INFUSIÓN CONTINUA

Las bases teóricas para el uso de la infusión continua son:

1. *La mayoría de las células tumorales colorrectales están en fase G0.*
2. *El 5-FU actúa cuando la célula está en fase S.*
3. *La vida media plasmática de 5-FU es de 13-14 minutos.*

Teniendo en cuenta esto, parece razonable pensar que si mantenemos en el tiempo niveles plasmáticos de 5-FU aumenta la probabilidad de que las células que se



encuentran en fase G0 pasan a fase S, sensible a la acción del citostático.

Los primeros trabajos con infusión continua se remontan a primeros años 60 . En 1975 se demuestra que la infusión continua durante 5 días permite administrar dosis altas de 5-FU, encontrando mayor tasa de respuestas . Se observa también un cambio en el patrón de toxicidad. En bolus la toxicidad limitante de dosis es la hematológica, mientras que en la infusión continua es la mucositis, apareciendo el síndrome mano-pie. Lockich demuestra en un ensayo fase 1, que se puede administrar 300 mg/m² en infusión continua durante 30 días con una toxicidad tolerable .

Los esquemas que incluyen una intensidad de dosis por encima de 2 g/m²/semana de 5-FU son los que consiguen una mayor tasa de respuestas, lo que confirma la hipótesis de Hryniuk referente a que es posible obtener mayor tasa si aumentamos la intensidad de dosis .

Seifert en 1975 publica los resultados de un estudio fase II en el que compara la actividad del 5-FU en bolus (12 mg/kg 1^o a 5^o día cada 29 días) con el 5-FU en infusión continua (30 mg/kg durante 120

horas cada 29 días) demostrando una mayor tasa de respuestas globales (22% frente a 44%) a favor de la infusión continua sin que estas diferencias fueran estadísticamente significativas. Posteriores estudios realizados por Lockich, Weinerman y Rougier lo confirman. Tan sólo en el estudio realizado por Lockich se encontraron diferencias significativas en cuanto a las respuestas (19). Respecto a la supervivencia no existen diferencias (**Tabla 1**).

Estos autores justifican la ausencia de diferencias en cuanto a supervivencia, con el hecho de que enfermos que fueron tratados con 5-FU bolus, pasaron tras progresar a tratarse con 5-FU en infusión continua.

El grupo cooperativo español para el tratamiento de tumores digestivos (TTD), en un estudio fase I-II, demostró que la dosis máxima tolerable en infusión continua de 48 horas semanal era de 3,5 g/m². Aunque el objetivo del estudio no fue la actividad se encontraron un 33% de respuestas, por lo que se comenzó un estudio fase II en el que se incluyeron 89 pacientes con carcinoma colorrectal avanzado. Se les administró 5-FU 3,5 g/m² en infusión continua de 48 horas semanal. La intensidad media de dosis

Tabla 1: *Cáncer colorrectal avanzado 5-FU: IC vs Bolus*

	N	Resp. Bolus	Resp. IC	Superviv. Bolus	IC
Seifert 1975	70	22%	44%	6m	6m
Lochick 1989	179	7%	30%	12m	13m
Weinerman 1990	170	7%	12%	9,5m	9,5m
ECOG 1992	450	19%	27%	11m	13m
Rougier 1992	155	8%	19%	9m	10m
TOTAL (media)	1024	8%	27%	NS	Croos-Over



recibida fue de 3 g/m². Las respuestas objetivas obtenidas fueron de un 38,5% (RC: 7/83, RP: 25/83, intervalo confianza para el 95%: 28-50%). La mediana de duración de la respuesta fue de 21 semanas, el tiempo medio a la progresión 30 semanas (tiempo mediano de seguimiento: 50 semanas), y la supervivencia media 56,5 semanas. La toxicidad limitante de dosis fue la diarrea (G3 =10%, G4 = 2%) y la mucositis (G3 = 11 %). Con el objeto de aumentar la actividad de 5-FU en IC se intentó la modulación bioquímica, para lo cual se diseñó un estudio fase II con 5-FU 3 g/m² IC 48 h semanal más leucovorín oral (15 mg/6 h durante la IC). Tras incluir 41 pacientes, la mitad presentaron toxicidad importante (diarrea G. III: 45%, C. IV: 14%. Náusea y vómitos G. IV: 17%), por lo que hubo que cerrar el estudio. La intensidad media de dosis recibida disminuyó de 3 g/m²/semana para la IC sin modular a 2,2 g/m²/semana para la IC modulada (en todos los pacientes hubo que reducir la dosis programada y en un 58% de los mismos se retrasó el tratamiento).

Posteriormente se inicio un nuevo estudio fase II con 5-FU 2 g/m² IC 48 h/semanal más LV a igual dosis que en el fase II realizado previamente. Se obtuvieron 37,5% de repuestas objetivas

(39/110), intervalo de confianza (28-46%), con un tiempo medio a la progresión de 7,6 meses y el tiempo mediano de supervivencia 14,5 meses, siendo la toxicidad limitante de dosis mucositis y diarrea. La intensidad media de dosis fue de 1,6 g/m² (25) (**Tabla 2**). Con estos estudios podemos concluir que cuando se utiliza el 5-FU a altas dosis no es necesario modular puesto que aumentamos la toxicidad sin aumentar la actividad. El siguiente paso en el grupo fue comparar el 5-FU 3,5 gr/m² infusión continua de 48 horas frente al esquema de la Clínica Mayo 5-FU 425 mg/ m² bolus más LV 20 mg/ m² cada 4 semanas, para ello se realizó un estudio fase III en el que se incluyeron un total de 306 pacientes. Las respuestas que se obtuvieron fueron del 19,2% para el 5-FU + LV y 30,3% para el 5-FU IC y estas diferencias fueron estadísticamente significativas (p<0.05). No encontramos diferencias ni en el tiempo a la progresión ni en la supervivencia. Con la llegada de los nuevos fármacos tales como Irinotecan y Oxaliplatino y con la intención de mejorar la actividad del 5-FU IC., se intentó su combinación con ambos fármacos.

En primer lugar se realizó dos estudios Fase II consecutivos con 5-FU IC + Oxaliplatino, el primero con 59 pacientes con 5-FU 3 gr/ m² IC de 48 sema-

Tabla 2: *Cáncer colorrectal avanzado. Experiencia con FU altas dosis +/- LV en el TTD*

ESQUEMA	Nº	RR	RC	RP	Sup. (m)	TP (m)
FU IC 3,5g/m ²	83	38,5%	8%	30	12,5m	6,6m
FU IC 3g/m ² + LV	43	29%	2,3%	26	13,7m	7m
FU IC 2g/m ² + LV	110	37,5%	2,8%	35	14,5m	7,5m
TOTAL (media)	236	35%	4,4%	30%	13,5m	7m



nal y Oxaliplatino 85 mg/m², una alta toxicidad (diarrea) nos hizo reducir un 25% la dosis de 5-FU por lo que el segundo fase II se realizó con 5-FU a la dosis de 2,25 gr/m².

Las respuestas que se obtuvieron fueron 55.9% y 63% respectivamente, al reducir la dosis se mantuvo la actividad, reduciéndose de manera importante la toxicidad grado _.

Respecto a la combinación 5-FU + Irinotecan en primer lugar se realizó un estudio fase I con 4 niveles de dosis de Irinotecan, manteniendo el 5-FU a 3 gr/m² estos fueron: 60, 70, 80 y 90 mg/m², en el 4º nivel (90 mgr) apareció toxicidad limitante de dosis (diarrea) por lo que la dosis que se propuso para el estudio fase II fue de CPT-11 80 mg/m² más 5-FU 3 gr/m² IC de 48 horas ambos fármacos semanales.

El estudio fase II de 5-FU + CPT-11 también necesito de dos cohortes la primera que la dosis anteriormente recomendada en el que se incluyeron 46 pacientes y sobre los que se obtuvieron unas tasas altas de respuesta 68% pero con una excesiva toxicidad grado _ (diarrea), por lo que igual que ocurrió en el estudio anterior de 5-FU+OXA fue necesario reducir la dosis de 5-FU, por lo que se empezó una segunda cohorte con 5-FU 2,25 gr/m² IC 48 horas más CPT-11 80 mg/m² ambos semanales, en este segundo estudio se incluyeron un total de 36 pacientes, las tasas de respuesta que se obtuvieron fueron de un 44% habiéndose reducido significativamente la toxicidad.

Actualmente el TTD está llevando a cabo dos estudios randomizados fase III el primero que compara nuestro esquema de 5-FU sólo más CPT-11 semanal contra el esquema de Douillard con 5-FU bolus e IC + LV + CPT-11 quincenal del que se han incluido unos 190 pacientes y el segundo

que compara nuestro esquema de 5-FU + OXA semanal frente al XELOX (Capecitabina más Oxaliplatino) de lo que se han incluido hasta el momento 170 pacientes; por otro lado en el último congreso de ASCO se han presentado los datos preliminares de un estudio fase I-II con la triple combinación (5-FU IC + Irinotecan + Oxaliplatino).

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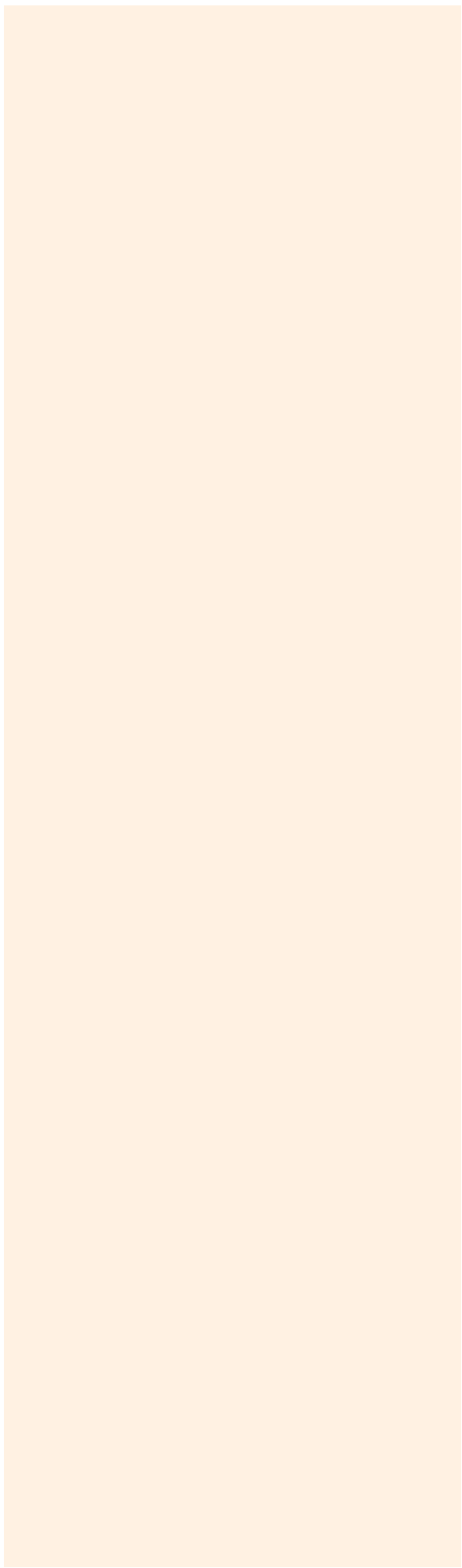
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Strategies to optimise chemotherapy in the treatment of advanced Colorectal cancer.

Alberto Sobrero

Medical Oncology Ospedale S. Martino,
Genova. *Italy*

ABSTRACT

There are 4 distinct scenarios that encompass the majority of advanced colorectal cancer patients. The first is the patient with stage IV disease limited to the liver or lung that is clearly resectable. While it is certainly correct to proceed with surgical resection right away, it must be remembered that 80% and of these patients will recur and die of this disease, therefore any treatment reducing the chances of recurring must be implemented. Since so far there is no randomized trial indicating a benefit of adjuvant treatment, evidence is lacking, although common sense may suggest that adjuvant chemotherapy may work in these conditions as well. Probably the best approach in these patients is to start chemotherapy for a short time period, to test for chemosensitivity and then, after response assessment, proceed to operation. The risk of this approach is to loose a potentially curable patient because of early progression, however, since the early progression rate with the commonly used doublets is around 10%, this risk is well balanced by the potential benefit of using the same CT as adjuvant in the postoperative period.

The second setting is the patient with the disease limited to the liver or lung , but extended enough to be considered non resectable. The goal of the treatment in this case should be tumor shrinkage to the point of making the disease resectable. This is not a common event (10-15% of patients), however, the endpoint is so highly relevant (resection and potential cure) that the choice of chemotherapy must be made with this in mind. Either doublet may be appropriate in this case, although most of the literature supporting this therapeutic intent has been generated



with oxaliplatin based regimens. Another potential choice in this case could be the triplet FU+oxaliplatin+irinotecan, although the triple combination are often too toxic.

The largest proportion of patients with stage IV present with non resectable disease. This group can be subdivided into 3 subgroups. Those in good conditions with good prognostic factors, those in suboptimal conditions and bad prognostic factors, and those in poor conditions and a short life expectancy. One may accept as a general rule that the three conditions are best treated with chemotherapy of decreasing intensity and toxicity: the doublets for the first, infusional FU or oral fluoropyrimidine for the second and either no treatment or an attempt with an oral fluoropyrimidine for the third one. This is certainly a correct general approach, however this is the area of most active debate. In fact all three conditions regard the palliative setting with no chance of cure and the oncologist could reason in the opposite way: aggressive approach for the bad prognosis and the lightest approach for the good prognosis patients. In deciding case by case which approach to take, one must consider the following factors: 1 the OS is now in the 20 months range thanks to the use of all three agents (FU, oxaliplatin and irinotecan), thus, if we take a light approach we are giving up chances of major palliation in a substantial proportion of patients. 2 in general the toxicity of doublets is higher than that of single agent fluoropyrimidine: since the toxicity and response rate is linked to the PS (PS is both prognostic and predictive), PS must be a major determinant of our choice. 3 PS may be low as a result of a rapidly growing tumor making the patient highly symptomatic, or may be low as the result of the progression

of the disease over a long time period (coupled with a decline in the general conditions): in the first case there is a clear indication for the doublets, in the second, for single agent CT. 4 The bulk of the disease including the number of metastatic sites is another determinant of success or failure and again the time factor may help under this regard.

Which CT to use first? The two doublets are clearly equivalent, so the choice may be based upon the different toxicity profile of folfox or folfiri. The real challenge is what to do if a patient starts with a doublet, and has SD after 4 months. Is it worth exploiting that combination until resistance (progression) or is it better to start earlier with the other doublet. These authors would favour the second approach. Another European school of thought suggests to continue with single agent infusional FU and then come back to the same original doublet (OPTIMOX). Rechallenge with the same combination? Yes as long as a response (or at least a long lasting SD) was obtained and enough time has elapsed since the last administration. In terms of further optimisation of CT strategies, once the concept of giving all three agents is fulfilled, little is to be gained by more sophisticated schedules. However we may improve quality of life by drug free period and this is an area of investigation at present. Oral fluoropyrimidine may take over infusional FU in the doublets. The future lies in the use of CT in combination with the targeted agents, either alone or in combination given continuously or sequentially in first second and third line.



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