A panel discussion of controversies and challenges in the adjuvant treatment of colon cancer

Eduardo Díaz-Rubio García, Albert Abad Esteve, Antonio Antón Torres, Enrique Aranda Aguilar, Manuel Benavides Ortega, Alfredo Carrato Mena, Andrés Cervantes Ruipérez, Jaime Feliu Batlle, Pilar García Alfonso, Jesús García Foncillas, Cristina Grávalos Castro, Matilde Navarro García, Fernando Rivera Herrero and José María Tabernero Caturía

Keywords: adjuvant treatment, colon cancer.

Current issues of adjuvant therapy for colon cancer concern the introduction of drugs other than fluorouracil/leucovorin (5-FU/L V), the benefits for stage II patients, the use of new primary endpoints and the influence of age on treatment benefits. These issues were addressed in a panel discussion and the conclusions were the following: FOLFOX4 is the first regimen that shows superiority over 5-FU/L V. The use of 3-year disease-free survival as primary endpoint could encourage the quicker adoption of improved therapeutic strategies into clinical practice. Available data suggest that there are some benefits for stage II patients, and the decision needs to be individualised for each patient. Further, therapeutic decisions based solely on the patient's age are inappropriate, and geriatric assessment tools will help in making this decision. This information would improve patient and physician understanding of the recent data regarding the potential benefits of adjuvant therapy.

Discusión de expertos sobre controversias y retos en el tratamiento adyuvante del cáncer de colon

Las controversias actuales referentes al tratamiento adyuvante del cáncer de colon incluyen la introducción de fármacos más allá de 5-FU/L V, el beneficio que ofrece a los pacientes con estadio II, el uso de nuevas variables y la influencia de la edad sobre los beneficios del tratamiento. Estas controversias fueron discutidas en un panel de expertos y las conclusiones fueron las siguientes: FOLFOX4 es el primer régimen que ha demostrado superioridad frente a 5-FU/L V. El uso de la supervivencia libre de enfermedad a 3 años como variable principal de los estudios podrá permitir una adopción más rápida de estrategias terapéuticas. Los datos disponibles sugieren que existe beneficio para los pacientes con estadio II, y la decisión terapéutica debe ser individualizada. Finalmente, también se llegó a la conclusión de que las decisiones basadas únicamente en la edad no son apropiadas, y las herramientas de valoración geriátrica servirán de apoyo. Esta información puede mejorar el entendimiento de pacientes y médicos acerca de los datos recientes relativos a los beneficios del tratamiento adyuvante.

Palabras clave: tratamiento adyuvante, cáncer de colon.

IMPLICATIONS OF RESULTS OF THE MOSAIC PHASE III CLINICAL TRIAL

The primary curative therapy of colon cancer is surgical resection. However, within the last 15 years, prospectively randomized appropriately powered cli-
Clinical trials have convincingly demonstrated that post-resection treatment, termed adjuvant therapy, is of benefit to all patients with node-positive disease (stage II) and arguably to high-risk node-negative (stage II) cases. The predominant single agent used as adjuvant therapy in colon cancer has almost universally been fluorouracil (5-FU). Attempts at modulating the activity of 5-FU with other compounds have been tried. A possible benefit from the use of levamisole in combination with 5-FU was suggested by a report from the North Central Cancer Treatment Group (NCCTG) and confirmed by the Intergroup study from the USA and a Dutch trial. The evidence that adjuvant therapy is effective in colon cancer was further demonstrated by controlled studies that compared 5-FU-leucovorin (L V) (folinic acid) treatment for 6 or 12 months with oxaliplatin. On the other hand, although there is no internationally accepted gold-standard 5-FU/L V regimen, the monthly 5-day bolus North Central Cancer Treatment Group/Mayo Clinic regimen has been commonly used as a reference treatment in phase III trials. However, when this regimen was compared with L V5-FU2, a bimonthly schedule of L V and bolus-plus-infusion 5-FU for 2 consecutive days every 2 weeks in the metastatic setting, L V5-FU2 proved superior in terms of response rate, progression-free survival, and toxicity, but not overall survival. Moreover, when this regimen was compared with the Mayo Clinic regimen in the adjuvant setting, toxicities were significantly lower in the L V5-FU2 group. A number of new agents of interest in colorectal cancer have been recently tested in clinical trials including the platinum compound oxaliplatin. Although it has been demonstrated that both cisplatin and carboplatin have no efficacy in advanced colon cancer, oxaliplatin—a platinum analogue with clinically insignificant renal and bone marrow toxicity—does have activity in advanced colon cancer. Oxaliplatin has been shown to enhance the response rate obtained with 5-FU, although limiting toxicities were neutropenia and peripheral neuropathy. In a phase II study, the effect of combining oxaliplatin with L V5-FU2 was assessed in 420 previously untreated patients with advanced measurable disease randomized to receive endoxan and bolus-plus-infusion 5-FU, either alone or combined with oxaliplatin (85 mg/m² as a 2-hour infusion on day 1). Patients allocated to oxaliplatin plus L V5-FU2 had significantly longer progression-free survival and better response rate when compared with the control arm. The improvement in overall survival did not reach significance probably due to the second-line treatments effect. L V5-FU2 plus oxaliplatin produced higher rates of neutropenia, grade 3/4 diarrhea, and grade 3 neurosensory toxicity, but this did not result in impairment of quality of life. In a recent randomized controlled trial, a total of 795 patients with previously untreated metastatic colorectal cancer were randomized to receive irinotecan and bolus fluorouracil plus leucovorin (IFL, control combination), oxaliplatin and infused fluorouracil plus leucovorin (FOLFOX), or irinotecan and oxaliplatin (IROX). The primary endpoint was time to progression. A median time to progression of 8.7 months, response rate of 45%, and median survival time of 19.5 months were observed with the FOLFOX regimen. These results were significantly superior to those observed for all endpoints in the IFL (6.9 months, 31%, and 15.0 months, respectively) and the IROX (6.5 months, 55%, and 17.4 months, respectively) groups. The FOLFOX regimen had significantly lower rates of severe nausea, vomiting, diarrhea, and febrile neutropenia. Sensory neuropathy and neutropenia were more common with the regimens containing oxaliplatin. It is concluded that the FOLFOX regimen of oxaliplatin and infused fluorouracil plus leucovorin was active and comparatively safe, and should be considered as a standard therapy for patients with advanced colorectal cancer. Additionally, in patients with metastatic colorectal cancer who progressed after IFL therapy, the second-line treatment with the combination of L V5-FU2 plus oxaliplatin was superior to treatment with L V5-FU2 in terms of response rate, time to tumor progression, and alleviation of tumor-related symptoms.

The MOSAIC trial

In 1998, a multicenter international randomized study of L V5-FU2 and oxaliplatin (FOLFOX4) compared to L V5-FU2 in stage II and II1 colorectal cancer (MOSAIC trial) was initiated in order to demonstrate the efficacy of the FOLFOX4 regimen in earlier stages of the disease with the goal to achieve a 25% decrease in the risk of recurrence at 3 years for patients receiving FOLFOX4 compared to those receiving L V5-FU2. The primary endpoint was disease-free survival (DFS) at 3 years, with survival and toxicity as secondary endpoints.

Patient eligibility

The eligibility criteria were stage II (Dukes’ stage B2 tumor, T3-4, N0, M0) and stage III (Dukes’ stage C tumor, T4, N1-2, M0) adenocarcinoma of the colon, age between 18 and 75 years, initiation of treatment within 7 weeks of a curative resection (without gross or microscopic evidence of residual disease), no prior treatment (chemotherapy, radiation therapy, or immunotherapy), and Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. Written informed consent was required and the study was approved by the ethics committees of all of the participating centers from 20 countries.