Rapid Evolution in Colorectal Cancer: Therapy Now and Over the Next Five Years

AIMERY DE GRAMONT
Hôpital Saint Antoine, Faubourg Saint Antoine, Paris, France

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LEARNING OBJECTIVES
After completing this course, the reader will be able to:

1. Discuss the public health importance and natural history of colorectal cancer.
2. Describe how treatments developed in the context of clinical trials have changed the prognosis of this disease.
3. Explain the potential impact of clinical trials on future treatment guidelines.

Abstract
A large number of patients with colorectal cancer have relatively early disease, and thus, adjuvant therapy has the potential to save lives. In stage III patients, there has been a steady improvement in 3-year disease-free survival with the use of 5-fluorouracil/leucovorin (5-FU/LV) regimens and capecitabine (Xeloda®; Hoffmann-La Roche Inc., Nutley, NJ, http://www.rocheusa.com) regimens. A median survival longer than 20 months was observed in patients with metastatic disease when treated with combination chemotherapy containing oxaliplatin (Eloxatin®; Sanofi-Synthelabo Inc., New York, http://www.sanofi-synthelabo.us) or irinotecan (Camptosar®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com). This has led to 5-FU/LV/oxaliplatin becoming standard therapy, along with 5-FU/LV/irinotecan. New data confirm the beneficial effect on disease-free survival of adding oxaliplatin to adjuvant colorectal cancer regimens based on 5-FU. These regimens show an effect when given in bolus as well as in infusional schedules. Interest in future adjuvant regimens focuses on the potential additional benefit of molecularly targeted agents, such as bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, http://www.gene.com), and on the ability of applied genomics to distinguish between high- and low-risk populations. The Oncologist 2005;10(supp 2):4–8

Adjuvant Therapy: The Past, or Fluoropyrimidines Alone
Colorectal cancer (CRC) is second only to breast cancer in the proportion of patients who have relatively early, and thus potentially curable, disease. For the 60%–70% of CRC patients who have stage II or III (Dukes’ B and C) tumors, adjuvant therapy has the potential to save lives [1,2]. Moertel et al. [3] found that stage III patients managed only by observation had a 3-year disease-free survival (DFS) rate of 52%. In the IMPACT trial, only 44% of patients in the observation group were alive and disease free at 3 years [4]. This situation was somewhat improved by the advent of

Correspondence: Aimery de Gramont, Hôpital Saint Antoine, 184, Faubourg Saint Antoine, 75571 Paris, Cedex 12, France. Telephone: 33-1-49282337; Fax: 33-1-49282344; e-mail: aimery.de-gramont@sat.aphp.fr Received September 5, 2005; accepted for publication September 5, 2005. ©AlphaMed Press 1083-7159/2005/$12.00/0

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bolus 5-fluorouracil (5-FU) and bolus 5-FU plus levamisole (Ergamisol®; Janssen Pharmaceutica Products, L.P., Titusville, NJ, http://www.janssen.com) or leucovorin [3,4]. Between 6 and 12 months of treatment was required, but benefit was proven even in the elderly population.

The Quick and Simple and Reliable (QUASAR) study represented a landmark because, for the first time, a trial was powered to demonstrate efficacy in stage II patients [5]. In that study, 3,239 stage II patients were randomized to receive either observation or treatment consisting of bolus 5-FU plus leucovorin, at high or low dose, or 5-FU plus levamisole. Of the patients in the observation group, 77.4% were alive at 5 years. Among patients receiving chemotherapy, the corresponding figure was 80.3%. The difference of 3% was statistically significant ($p = .02$).

The GERCOR C96-1 study, in which 905 stage II or III patients were randomized to receive one of two 5-FU/LV regimens (LV5FU2 or FUFOL) (each for 24 or 36 weeks), was important in demonstrating the equivalent efficacy of infusional and bolus 5-FU in the adjuvant setting. In both groups, 73% of patients were alive and disease-free at 4 years (hazard ratio [HR], 1.03), but the infusion regimen was better tolerated and so has become the treatment standard [6]. That study had additional importance in that it validated LV5FU2 as the control arm for the next generation of studies using oxaliplatin (Eloxatin®; Sanofi-Synthelabo Inc., New York, http://www.sanofi-synthelabo.us) and irinotecan (Camptosar®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com).

In the Xeloda® in Adjuvant Colon Cancer Therapy (X-ACT) trial, conducted between 1998 and 2001, nearly 2,000 stage III patients received 24 weeks of adjuvant treatment using either the Mayo regimen or the oral 5-FU prodrug capecitabine (Xeloda®; Hoffmann-La Roche Inc., Nutley, NJ, http://www.rocheusa.com) [7]. The 3-year survival rate with capecitabine was 64.2%, compared with 60.6% for the Mayo regimen (HR, 0.87; $p = .053$). By per-protocol analysis, the HR was 0.89.

Overall, the active treatment of stage III patients has seen a steady improvement in the 3-year DFS of around 50% compared with observation alone. Among five recent studies of 5-FU/LV regimens, 3-year DFS rates ranged from 61%–67% [4, 8–10]. In capecitabine-treated patients in the X-ACT trial, it was 64%, that is, within the range seen with 5-FU.

One pertinent question is whether we should be using 5-FU infusions, which need a catheter and pump, or capecitabine, which is more convenient but not without side effects. The two modalities have still not been directly compared.

The relapse rate for CRC is relatively high in the first 2 years (perhaps 10%–14% per year), but it falls to <5% at year 5 (Fig. 1). Eighty percent of relapses occur within the first 3 years. Importantly, the 3-year DFS rate is highly correlated ($r = 0.88$) with survival at five years [11]. This has encouraged the U.S. Food and Drug Administration to accept 3-year DFS as the end point of adjuvant studies, and should speed the introduction of new agents active in the adjuvant setting.

**The Present, or Combination Chemotherapy**

In patients with metastatic disease, several studies of combination chemotherapy containing oxaliplatin or irinotecan have shown median survival times longer than 20 months [12–15]. The 5-FU/LV/oxaliplatin regimens FOLFOX4 and FOLFOX7 have become standard therapy, along with the 5-FU/LV/irinotecan regimen FOLFIRI (Fig. 2) [16, 17].

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**Figure 1.** The relapse rate for colorectal cancer is highest in the first 2 years.

**Figure 2.** Summary of current treatments for metastatic colorectal cancer: progression-free survival (PFS) versus toxicity.
In the adjuvant arena, the DFS rates comparing bolus 5-FU/LV alone with irinotecan plus bolus 5-FU/LV (IFL) were similar in the two arms, with a nonsignificant advantage for 5-FU/LV ($p = .81$) [18].

The results of the Pan-European Trial in Adjuvant Colon Cancer (PETACC)-3/V307 and ACCORD1, were presented at the 2005 annual meeting of the American Society of Clinical Oncology (ASCO). Both studies involved infusional 5-FU regimens (LV5FU2 or AIO) and irinotecan. PETACC-3 included 3,278 patients and ACCORD1 included 400 patients, but these patients were at particularly high risk [19, 20]. Both studies failed to show a significant advantage for irinotecan-based regimens.

**MOSAIC Updates**

In the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study, 2,246 patients (40% with stage II disease and 60% with stage III disease) were randomized to receive either FOLFOX4 or LV5FU2 [10, 21]. Data from January 2005, representing a median follow-up of 56.2 months were presented at the 2005 ASCO Annual Meeting. They, therefore, extend the information presented earlier.

The FOLFOX4 arm showed a 6.6% advantage in DFS. Among stage III patients, 73% were alive and disease free at 3 years. The overall improvement in DFS of 8.6% in this population must be considered when the results of comparable trials are reviewed.

For stage II patients, the benefit was 3.5%, and for stage III patients it was 8.6%. Among stage III N1 patients with fewer than four lymph nodes involved, the difference in DFS was 7.2%, but it was 11.5% among stage III N2 patients with four or more nodes involved. Interestingly, the pattern of disease recurrence with time was the same in the FOLFOX4 and LV5FU2 groups. Overall, there was a 2.1% difference between arms in overall survival. But 7.4% of the patients were alive with relapse in the FOLFOX4 arm versus 11.9% in the LV5FU2 arm. With this difference in patients alive with recurrence added to what has already been observed, there is no doubt that the final difference in survival will be significant.

The principal hematological toxicity with FOLFOX4 is neutropenia; 41% of patients experienced grade 3/4 toxicity, but fewer than 2% had febrile neutropenia or neutropenic sepsis. Gastrointestinal toxicities were generally mild. The major nonhematological toxicity was neuropathy, but this is something from which patients can recover. Of 146 patients with grade 3 neuropathy, almost all recovered: 20% remained grade 1 or 2. The pattern was similar for grade 2 neuropathy. However, it is important to note that careful clinical assessment can prevent patients developing severe neuropathy. Toxic deaths were 0.5% in both arms.

The updated MOSAIC data show that the benefit in terms of DFS seen at 3 years is confirmed with a further year of follow-up. At a median follow-up of 4 years, a 24% lower relative risk for relapse was observed in patients who received FOLFOX4 rather than LV5FU2. However, survival data are not yet mature. Importantly, for the evaluation of toxicity, the MOSAIC trial data show that there are late recoveries from sensory neuropathy.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 data firmly reinforce the results of the MOSAIC trial [22]. Patients were randomly assigned to LV-modulated bolus 5-FU alone or with the addition of oxaliplatin (FLOX). The latter group enjoyed a significantly greater chance of DFS at 3 years (76.5% versus 71.6%; $p < .004$). That study is important in demonstrating that oxaliplatin is of benefit even in bolus 5-FU regimens. However, the toxicity profile again favors 5-FU infusional regimens, especially for further combinations with new drugs.

In the capecitabine plus oxaliplatin (XELOX) NO16969 trial, the Mayo LV5FU bolus regimen is being compared with a capecitabine plus oxaliplatin regimen in 1,850 patients with stage III disease. Results for the primary end point of DFS are expected in 2006. The study may well be positive, but interest will center on the extent of the difference between treatments. Figure 3 illustrates the evolution of adjuvant chemotherapy.

**The Future**

Interest in future therapies centers on the potential contribution of targeted agents such as vascular endothelial growth factor (VEGF) inhibitors, notably the antiangiogenic bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, USA).

![Figure 3. Evolution of adjuvant therapy of colon cancer.](image-url)

In a first-line phase III trial, the addition of bevacizumab to IFL resulted in a longer median progression-free survival time of 10.6 months, versus 6.2 months [23]. In another study in second-line metastatic CRC, patients were randomized to receive either FOLFOX4, FOLFIRI4 plus bevacizumab, or bevacizumab alone. Overall survival was 12.5 months in the combination arm, compared with 10.2 months with bevacizumab alone and 10.7 months with FOLFOX4 alone. The HR in patients in whom bevacizumab was added to standard therapy was 0.74, \( p = .0024 \).

The results of the BOND trial, in which patients with EGFR-positive tumors refractory to 5-FU plus irinotecan were randomized to receive either irinotecan plus cetuximab or cetuximab followed by irinotecan, are also available [25]. Data suggest that the simultaneous use of an antibody and a cytotoxic agent is more active than their sequential administration (median progression-free survival time of 4.1 months compared with 1.5 months).

Such findings have led to two major ongoing trials. In the AVANT study (BO17920), patients with stage II or III CRC are randomized to one of three arms: (a) FOLFOX4 for 24 weeks followed by observation; (b) FOLFOX4 plus bevacizumab for 24 weeks followed by bevacizumab monotherapy for a further 24 weeks; and (c) XELOX plus bevacizumab followed by bevacizumab monotherapy, both for 24 weeks. In the second major study, NSABP C-08, stage II/III patients are being randomized to either the modified FOLFOX6 regimen for 24 weeks or modified FOLFOX6 plus bevacizumab followed by 24 weeks bevacizumab. Both studies are accruing strongly and are likely to be completed within 2 years.

There is also a particularly intelligent adjuvant study (ES202) in which genetic features are used to classify stage II patients into low- and high-risk categories. Patients with microsatellite instability and normal 18q, judged to be at low risk, receive no therapy. Patients with microsatellite stability and loss of heterozygosity at 18q are randomized to receive either FOLFOX or FOLFOX plus bevacizumab.

Among questions that remain to be resolved are those relating to the duration of adjuvant chemotherapy, the potential benefits to be derived from combining FOLFOX with FOLFIRI, and the role of XELOX4 versus classical XELOX. Regarding molecularly targeted drugs, we have yet to assess the optimum duration of therapy, the possible gain by combining EGFR and VEGF inhibitors, and how best to use them with cytotoxics. With both classes of agent, genetic and pharmacogenomic studies are needed to identify subsets of patients most likely to benefit from particular forms of treatment.

**Disclosure of Potential Conflicts of Interest**

Prof. de Gramont has received honoraria from sanofi-aventis, Roche, and Baxter and has acted as a consultant for sanofi-aventis and Roche.

**References**

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