Update on Targeted Agents for Adjuvant Treatment of Colon Cancer in 2006

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ABSTRACT

Due to its frequency and still too high mortality rate, colorectal cancer represents a major public health problem. The use of adjuvant chemotherapy has improved the prognosis for patients with this disease. Adjuvant chemotherapy regimens derive from the most active regimens in advanced colorectal cancer therapy. Recently, two monoclonal antibodies have shown activity in patients with advanced colorectal cancer: bevacizumab, which targets vascular endothelial growth factor (VEGF), has shown activity as first- and second-line therapy; and cetuximab, which targets the epidermal growth factor receptor (EGFR), has demonstrated activity as third-line therapy. The objective of this paper is to present the ongoing trials evaluating targeted therapies in adjuvant treatment for colon cancer. Duration of therapy, new agents, and combinations of targeted therapies are other critical issues for the future.

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Despite advances in the treatment of colorectal cancer, the mortality rate remains high and the disease continues to represent a major public health issue. In Western countries, the mortality rate is still close to 40%. The value of adjuvant treatment of colon cancers was clearly demonstrated only in the early 1990s.[1] The combination of 5-fluorouacil plus folinic acid (5-FU/FA) became standard treatment for stage III colon cancers a few years later, with the use of such treatment for patients with stage II disease being controversial.[2–4] The therapeutic potential of systemic treatments for colorectal cancer has expanded rapidly during the past 10 years with the introduction of oral fluoropyrimidines, oxaliplatin, and irinotecan. The oral fluoropyrimidine capecitabine, uracil/tegafur (UFT) plus leucovorin (LV), as well as infusional 5-FU/LV are at least as effective as bolus 5-FU/LV and are associated with less toxicity.[5–7]

While combinations of irinotecan with either 5-FU bolus or 5-FU infusion failed to demonstrate superiority over 5-FU/FA alone,[8–10] results with oxaliplatin were positive.

The international MOSAIC trial first demonstrated the superiority of oxaliplatin added to infusional 5-FU/FA in the FOLFOX4 regimen over the infusional 5-FU/FA combination.[11,12] In 2004, the FOLFOX4 combination became the new standard for adjuvant treatment of stage III colon cancer. FOLFOX4 is generally well tolerated; the principal complication is peripheral sensory neuropathy, which is reversible in the majority of cases. Similarly, the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial also showed a significant improvement in 3-year disease-free survival when oxaliplatin was added to bolus 5-FU/LV in the FLOX regimen as compared with 5-FU/LV alone (Roswell Park regimen).[13]

Use of adjuvant chemotherapy for stage II colon cancer is still being debated. Most studies performed, including the MOSAIC trial, generally lacked the power to demonstrate a statistically significant difference in this heterogeneous population of patients, despite a strong trend in favor of chemotherapy in most cases. Prognostic factors and co-morbidities should be taken into account in evaluating the risk:benefit ratio, as an aid in determining the therapeutic strategy for each patient. Prognostic and predictive factors routinely used today are histologic stage (T), lymph-node involvement (N), number of lymph nodes examined in the resected tissue, tumor perforation of the intestinal wall, degree of tumor differentiation, and invasion of the lymphatic and/or vascular systems. The prognostic value of intestinal occlusion remains controversial.

At the same time, advances in tumor biology have led to the discovery of new biologic markers, such as microsatellite instability (MSI) and loss of heterozygosity (LOH), which may be predictive of tumor response to cytotoxic agents. This is particularly valuable in the context of stage II colorectal cancer, where the benefit of adjuvant cytotoxic therapy is more controversial. MSI and LOH are currently being investigated in a prospective trial.

The angiogenesis inhibitor bevacizumab and the epidermal growth factor receptor (EGFR) inhibitor cetuximab have shown activity when combined with 5-FU/LV–based regimens as first-line treatment of advanced disease and are currently being evaluated as part of adjuvant therapy in colorectal cancer.

ADJUVANT TARGETED THERAPIES: EVIDENCE FROM THE ADVANCED-DISEASE SETTING

Bevacizumab

Clinical trials have demonstrated synergistic effects of bevacizumab combined with chemotherapy. In addition, direct antivascular effects and the potential suppression

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of an angiogenic switch of micrometastases shown in laboratory studies of bevacizumab support its use both combined with chemotherapy and as a single agent.[14–16]

In a phase III trial of first-line therapy, the addition of bevacizumab to the irinotecan/5-FU/LV (IFL) regimen in patients with metastatic colorectal cancer resulted in a 29% increase in response rate compared with IFL alone (IFL, 35%; IFL plus bevacizumab, 45%) and a 70% increase in median progression-free survival (IFL, 6.2 months; IFL plus bevacizumab, 10.6 months).[17] Bevacizumab added to FOLFOX has also shown activity in the first- and second-line settings with an acceptable toxicity profile. In the TREE-2 study, first-line FOLFOX plus bevacizumab resulted in a 53% response rate and a 9.9-month median progression-free survival duration in a series of 70 patients with metastatic colorectal cancer.[18] Recent results from the large randomized NO16966 study suggested that bevacizumab added to FOLFOX or capecitabine/oxaliplatin (XELOX) improved median progression-free survival by 20%.[19] In a phase III comparison of FOLFOX vs. FOLFOX plus bevacizumab as second-line therapy, response rate more than doubled in the bevacizumab arm relative to FOLFOX alone (21.8% vs. 9.2%, respectively) and median progression-free survival increased by 50% (7.2 vs. 4.8 months, respectively).[20]

The addition of bevacizumab does not exacerbate side effects specific to the chemotherapy regimen. Bevacizumab-related adverse effects are usually moderate, with the exception of arterial thromboembolic events and bowel perforation, which occurred in fewer than 2% of patients.[17,18]

Cetuximab

Cetuximab was found to be active as a single agent and to potentiate irinotecan effects when used in second-line therapy for metastatic colorectal cancer in the randomized BOND trial.[21] Preliminary results of a small European study (ACROBAT trial) of first-line treatment with 5-FU/LV/oxaliplatin (FOLFOX4) and cetuximab showed a response rate of 81% and progression-free survival of 12.3 months.[22] In a similar US study evaluating the addition of cetuximab to a modified FOLFOX6 regimen in 82 patients, preliminary results indicate a 53% response rate.[23] Phase III trials assessing cetuximab combined with FOLFOX in the first-line setting, and combined with irinotecan in the second-line setting, are ongoing.

Data indicate that cetuximab might increase the incidence of chemotherapy-induced diarrhea. Cetuximab-specific adverse effects include allergy, which was grade 3/4 in 1% of patients, and the more burdensome rash/acne in 10% to 15% of patients.[21,22]

Other Candidate Targeted Therapies

As yet, trials evaluating targeted agents other than bevacizumab and cetuximab in the adjuvant setting are lacking. However, some agents being tested in phase II or III studies in advanced disease are potential candidates for future adjuvant therapies.[24] One such agent is panitumumab, another monoclonal antibody targeting EGFR, which is being evaluated in a phase III trial of first-line therapy for advanced colorectal cancer. Potential advantages of this human monoclonal antibody over cetuximab are fewer allergic reactions, and a longer half-life allowing longer intervals between treatment cycles. Other candidate agents are tyrosine kinase inhibitors, especially those targeting VEGF or EGFR. Randomized studies of PTK-ZK in first- and second-line therapy were negative; however, new, potentially more potent drugs are in phase II evaluations in advanced disease, including erlotinib, sorafenib, XL999, BIBF1120, BIBW 2992, ZD2171 and sunitinib. Imatinib is also being evaluated in combination with capecitabine. Among other targeted therapies, histone deacetylase inhibitors (suberoylanilide hydroxamic acid [SAHA]) and PKC-β inhibitors are being assessed in phase II studies.

ONGOING STUDIES OF ADJUVANT THERAPY IN COLORECTAL CANCER

Ongoing studies of adjuvant chemotherapy for colorectal cancer have integrated biologic approaches into the therapeutic strategy, including assessment of MSI and LOH, and use of anti-EGFR antibodies (cetuximab) or anti-VEGF antibodies (bevacizumab) with conventional chemotherapy regimens.

Bevacizumab in the Adjuvant Setting

The demonstrated efficacy of bevacizumab in patients with metastatic disease has led to its evaluation in two large trials of adjuvant therapy. The AVANT trial has a target enrollment of 3,450 patients with high-risk stage II or stage III disease. Patients are randomly assigned to one of three treatment arms. The FOLFOX4 regimen administered during 24 weeks is serving as the reference treatment. Other treatment arms are FOLFOX4 plus bevacizumab for 24 weeks followed by bevacizumab alone for 24 weeks; and XELOX plus bevacizumab for 24 weeks followed by bevacizumab alone for 24 weeks. Bevacizumab is administered every 2 or 3 weeks. The primary end point of the trial is 3-year disease-free survival in patients with stage III disease only.

The NSABP C-08 study, with an estimated total of 2,700 patients, delivers modified FOLFOX6 for 24 weeks, or modified FOLFOX6 plus bevacizumab for 24 weeks followed by maintenance treatment with bevacizumab alone for 24 weeks. The primary objective of the study is 3-year DFS in patients with both stages II and III disease.

The trial designs for both AVANT and NSABP C-08 aim to exploit the synergistic effect of bevacizumab in combination with chemotherapy as well as the direct anti-vascular effects of bevacizumab as a single agent. However, the requirement of a prolonged administration — without interruption — of bevacizumab has not been established. This is in contrast to studies of stop-go or treatment interruption strategies with conventional chemotherapy, which have been shown feasible in patients with colorectal cancer.[25,26]

In addition to these trials, the QUASAR-2 trial in the United Kingdom is evaluating bevacizumab plus capecitabine vs. capecitabine alone in a target population of 2,240 patients with stage III colorectal cancer. Of note, this trial denies stage III patients the proven benefit of oxaliplatin therapy. The US study, E5202, in addition to evaluating bevacizumab in the adjuvant setting, is testing a therapeutic strategy based on each patient's MSI and LOH status. After surgery, 3,125 patients will be stratified according to MSI and LOH. "Low-risk" patients in terms of metastatic relapse (MSI and LOH–) receive no adjuvant treatment (observation arm), whereas "high-risk" patients (MSS [microsatellite-stable]

and LOH+) receive modified FOLFOX6 with or without bevacizumab.

Cetuximab in the Adjuvant Setting

In the PETACC 8 trial being conducted in Europe, 2,000 colorectal cancer patients receive FOLFOX4 for 24 weeks or FOLFOX4 plus cetuximab for 24 weeks. The US North Central Cancer Treatment Group N0147 study is similarly comparing modified FOLFOX6 with or without cetuximab for 24 weeks in 2,300 patients. Of note, both studies include only stage III patients and cetuximab is administered weekly and only during chemotherapy. Patients are not required to have EGFR-positive primary tumors to be eligible to receive cetuximab therapy.

CONCLUSION

Two monoclonal antibodies, bevacizumab and cetuximab, which have demonstrated activity in advanced colorectal cancer therapy, are now being evaluated in large randomized studies in the adjuvant setting. Initial results are expected in 2008 or 2009. The preclinical and clinical rationales for use of bevacizumab therapy are particularly strong. Biologic prognostic factors (eg, MSI, LOH) are now being evaluated in prospective studies and may in the future help to better identify colorectal cancer patients most likely to benefit from adjuvant chemotherapy.

REFERENCES

1. Moertel CG, Fleming TR, Macdonald JS, et al: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 322:399–401, 1990
2. IMPACT investigators: Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 345:939–944, 1995
3. Haller DG, Catalano PJ, Macdonald JS, et al: Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer/ final report of Intergroup 0089. *J Clin Oncol* 23:8671-8678, 2005
4. Wolmark N, Rockette H, Mamounas E, et al: Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin and levamisole, in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project protocol C-04. *J Clin Oncol* 17:3553–3559, 1999
5. André T, Colin P, Louvet C, et al: Semimonthly vs. monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: results of a randomized trial. *J Clin Oncol* 21:2896–2903, 2003
6. Twelves C, Wong A, Nowacki MP, et al: Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 352:2696–2704, 2005
7. Lembersky BC, Wieand HS, Petrelli NJ, et al: Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. *J Clin Oncol* 24:2059–2064, 2006
8. Saltz LB, Niedzwiecki D, Hollis D, et al: Irinotecan plus fluorouracil/leucovorin (IFL) versus fluorouracil/leucovorin alone (FL) in stage III colon cancer (Intergroup trial CALGB C89803). 2004 ASCO Annual Meeting Proceedings. *J Clin Oncol* 22:14S, 2004 (abstr 3500)
9. Ychou M, Raoul J, Douillard J, et al: A phase III randomized trial of LV5FU2+CPT-11 vs. LV5FU2 alone in adjuvant high risk colon cancer (FNCLCC Accord02/FFCD9802). 2005 ASCO Annual Meeting Proceedings. *J Clin Oncol* 23:16S, 2005 (abstr 3502)
10. van Cutsem E, Labianca R, Hossfeld D, et al: Randomized phase III trial comparing infused irinotecan/5-fluorouracil (5-FU)/folinic acid (IF) versus 5-FU/FA (F) in stage III colon cancer patients (pts) (PETACC 3). 2005 ASCO Annual Meeting Proceedings. *J Clin Oncol* 23:16S, 2005 (abstr 8)
11. André T, Boni C, Mounedji-Boudiaf L, et al: Oxaliplatin, 5-fluorouracil and leucovorin as adjuvant treatment of colon cancer: results of the international randomized MOSAIC trial. *N Engl J Med* 350:2343–2351, 2004
12. de Gramont A, Boni C, Navarro J, et al: Oxaliplatin/5FU/LV in the adjuvant treatment of stage II and stage III colon cancer: efficacy results with a median follow-up of 4 years. 2005 ASCO Annual Meeting Proceedings. *J Clin Oncol* 23:16S, 2005 (abstr 3501)
13. Wolmark N, Wieand HS, Kuebler JP, et al: A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: results of NSABP Protocol C-07. 2005 ASCO Annual Meeting Proceedings. *J Clin Oncol* 23:16S, 2005 (abstr 3500)
14. Warren RS, Yuan H, Matli MR, et al: Regulation by vascular endothelial growth factor of human colon cancer tumorigenesis in a mouse model of experimental liver metastasis. *J Clin Invest* 95:1789–1797, 1995
15. Willett CG, Boucher Y, Di Tomaso E, et al: Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med* 10:145–147, 2004
16. Yuan F, Chen Y, Dellian M, et al: Time-dependent vascular regression and permeability changes in established human tumor xenografts induced by an anti-vascular endothelial growth factor/vascular permeability factor antibody. *Proc Natl Acad Sci U S A* 93:14765–14770, 1996
17. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 350:2335–2342, 2004
18. Hochster HS, Hart LL, Ramanathan RK, et al: Safety and efficacy of oxaliplatin/ fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): final analysis of the TREE study. 2006 ASCO Annual Meeting Proceedings. *J Clin Oncol* 24:18S, 2006 (abstr 3510)
19. Cassidy J, Clarke S, Diaz-Rubio E, et al: XELOX vs. FOLFOX4: Efficacy results from XELOX-1/ NO16966, a randomized phase III trial in first-line metastatic colorectal cancer (MCRC). 2007 ASCO Gastrointestinal Cancers Symposium; January 19–21, 2007; Orlando, FL (abstr 270)
20. Giantonio BJ, Catalano PJ, Meropol NJ, et al: High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200. 2005 ASCO Annual Meeting Proceedings. *J Clin Oncol* 23:16S, 2005 (abstr 2)
21. Cunningham D, Humblet Y, Siena S, et al: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 351:337–345, 2004
22. Tabernero J, Van Cutsem E, Sastre J, et al: An international phase II study of cetuximab in combination with oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX-4) in the first-line treatment of patients with metastatic colorectal cancer (CRC) expressing epidermal growth factor receptor (EGFR). 2004 ASCO Annual Meeting Proceedings. *J Clin Oncol* 22:14S, 2004 (abstr 3512)
23. Dakhil S, Cosgriff T, Headley D, et al: Cetuximab + FOLFOX6 as first-line therapy for metastatic colorectal cancer. 2006 ASCO Annual Meeting Proceedings. *J Clin Oncol* 24:18S, 2006 (abstr 3557)
24. Availble at: http://www.cancer.gov/clinicaltrials
25. Tournigand C, Cervantes A, Figer A, et al: OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer: a GERCOR study. *J Clin Oncol* 24:394–400, 2006
26. Maindrault-Goebel F, Lledo G, Chibaudel B, et al: OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC): a GERCOR study. 2006 ASCO Annual Meeting Proceedings. *J Clin Oncol* 24:18S, 2006 (abstr 3504)

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