Accomplishments in 2008 in the Treatment of Advanced Metastatic Colorectal Cancer

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I. OVERVIEW OF THE DISEASE

I-A. Incidence

Colorectal cancer (CRC) continues to be the fourth most commonly diagnosed cancer worldwide and accounts for the second highest cancer-related mortality rate.[1]

I-B. Predictive Biomarkers

In recent years, the introduction of predictive biomarkers has provided clinicians with a more rational way to select from the different systemic therapy options and discern those that are more likely to benefit their CRC patients.

The number of circulating tumor cells (CTCs) before and during treatment of metastatic CRC (mCRC) has been shown to be an independent predictor of progression-free survival (PFS) and overall survival (OS).[2] The prognostic value of CTCs has been confirmed in other studies.[3]

Anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab and panitumumab) have been introduced in the treatment of metastatic CRC, initially in the refractory setting and now as first-line treatment. *K-ras* mutations in codons 12 and 13 were shown to predict primary resistance to these compounds. This predictive effect of *K-ras* mutations was originally described in retrospective evaluations.[4–8] Subsequently, this effect was confirmed in the context of phase III studies when cetuximab[9] or panitumumab[10] was compared with best supportive care. The results of two randomized studies evaluating the clinical efficacy of cetuximab combined with standard first-line chemotherapy regimens (FOLFIRI [5-fluorouracil (5-FU), leucovorin, irinotecan] and FOLFOX [5-FU, leucovorin, oxaliplatin]) have been presented. In the first-line setting, the predictive biomarker role of *K-ras* mutation status has been reproduced.[11,12] The evidence of the predictive role of *K-ras* mutations in treating patients with either cetuximab or panitumumab is consistent within all the different studies (either cohorts or randomized) and in the different settings (refractory setting and first-line).

As not all patients with wild type *K-ras* mutations benefit from treatment with anti-EGFR monoclonal antibodies, research to identify other predictive biomarkers of response or primary resistance to these compounds continues. *B-raf* is downstream from *K-ras* and has been identified as an additional biomarker of resistance. Those patients with metastatic CRC that bear *B-raf* mutations do not benefit from treatment with anti-EGFR monoclonal antibodies.[13] Mutations in the *PIK3CA* gene have been shown to produce resistance to cetuximab in preclinical models,[14] although the potential role in the clinical setting is more controversial.[15] The same consideration applies to PTEN loss of function with evidence of resistance in preclinical models,[14] and some suggestions in the same direction in the clinical setting, although this has not been definitively

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addressed.[15–17] *EGFR* gene copy number had been described as a potential biomarker predicting response to EGFR inhibitors, in particular in patients with non-small cell lung cancer. However, recent data have established its usefulness in patients with metastatic CRC being treated with cetuximab,[18] although this continues to be a controversial topic. Finally, some studies have suggested that particular polymorphisms of COX-2, EGF and EGFR may have a predictive value of efficacy for cetuximab-based treatment in patients with metastatic CRC.[19,20] Nevertheless, beside the well-established predictive value of *K-ras* mutations for the treatment of metastatic CRC patients with anti-EGFR monoclonal antibodies, all the other suggested biomarkers need further confirmation and standardization before being applied routinely in the clinical setting.

Cytotoxic agents may also have potential predictive biomarkers of activity. Polymorphisms in the excision repair cross-complementing 1 *(ERCC1)* gene have been evaluated for prediction of resistance or sensitivity to oxaliplatin-based chemotherapy used as first-line treatment in mCRC. The results of these studies have been inconclusive, as some studies support the hypothesis that certain *ERCC1* polymorphisms may enhance DNA repair and therefore diminish the activity of oxaliplatin-based chemotherapy,[21,22] whereas others do not.[23] The expression by immunohistochemistry of Topo1 has identified subpopulations that did or did not benefit from irinotecan; only patients whose tumors had high expression benefited from this cytotoxic treatment.[23] Nevertheless, these results have to be confirmed in other studies; the limitations that immunohistochemistry has in terms of reproducibility has to be considered in these trials.

II. CURRENT GENERAL THERAPY STANDARDS

In the United States and Europe, the standard of care for first-line treatment of metastatic disease is combination therapy. Regimens used most commonly are based on either irinotecan or oxaliplatin given with 5-FU or capecitabine. Regarding biologics, bevacizumab is used in most cases and cetuximab is being progressively introduced in some European countries. This preference is based on data from randomized studies conducted in previous years.

III. ACCOMPLISHMENTS DURING THE YEAR

III-A. Combined Modality Management of Liver Metastases

CRC is unusual among solid tumors in that metastatic disease is potentially curable. Early case series in the 1980s and 1990s established the curability of oligometastatic disease treated with surgical resection. Patient selection for a surgical approach to liver metastasis was typically based on prognostic features such as number and size of metastases, unilobar versus bilobar disease, and disease-free interval from primary resection. As surgical techniques have improved and long-term follow-up of surgically treated patients with poor prognostic indicators has shown a significant potential for disease-free survival, the recent trend has been to evaluate suitability for resection in terms of how much functional liver will be left behind rather than how much will be removed.

Although cure is possible following surgical resection of metastases in liver or lung, the majority of patients are still destined to suffer local and/or distant disease recurrence. With improvements in the adjuvant therapy of stage II and III CRC, the natural question arose as to whether systemic therapy could improve outcome when added to surgical management of metastatic disease.

- This hypothesis was recently addressed by the EORTC Intergroup trial 40983.[24] Nordlinger et al reported the results of this prospective phase III trial, in which 364 patients with four or fewer resectable liver metastases were randomized to treatment with surgery alone or surgery plus perioperative systemic chemotherapy. Patients in the systemic therapy group received six courses of FOLFOX4 before and six courses after metastasectomy. The primary end point was PFS. The intent-to-treat analysis indicated an absolute increase of 7.3% in rate of 3-year progression-free survival (PFS), with a hazard ratio of 0.79 (95% confidence interval [CI] 0.62–1.02), $P = .058$. When only eligible patients were considered, the increase in PFS at 3 years was 8.1%, with HR 0.77 [CI 0.60–1.00, $P = .041$). Preoperative treatment was associated with a moderate increase in postoperative morbidity. Although the improvement in PFS did not reach statistical significance in the intent-to-treat analysis, the trend was consistent with the underlying hypothesis. It is likely that the investigators overestimated the potential benefit of perioperative therapy in designing the trial, such that the sample size was simply too small to definitively identify a modest, but clinically meaningful, benefit associated with treatment. Given these study results and the established benefit of adjuvant therapy in the non-metastatic high-risk setting, it is not likely that a larger randomized trial will be possible to clarify the benefit of systemic treatment when added to surgical resection of metastases. Ongoing and future studies will address the selection of systemic regimens, scheduling of perioperative treatment, and the selection of patients for pre- or post-operative therapy, including those deemed "potentially resectable" if they experience an antitumor response.
- Folprecht et al[25] recently reported preliminary results of the CELIM trial. In this trial, patients with unresectable liver metastases were randomly assigned to receive 4 months of weekly cetuximab with either FOLFOX or FOLFIRI. The primary end point was response rate, with secondary end points including R0 resection rate after induction chemotherapy and PFS. A total of 111 patients were randomized; *K-ras* mutation analysis was not an eligibility criterion. Response rates were 85% and 66%, and R0 resection rates were 37% and 34%, in the FOLFOX and FOLFIRI arms, respectively. These data support the notion that some patients with "unresectable" hepatic metastases can be "converted" to resectability with neoadjuvant treatment. Larger studies with adequate follow up are required to fully define the effect of this approach on long-term survival.
- (For more information on reports in 2008 on management of potentially curable metastatic CRC, see the article by Adam et al, *Accomplishments in 2008 in the Management of Curable Metastatic Colorectal Cancer,* in this issue (page S15).[26]

III-B. Treatment of Advanced Disease

III-B. 1. Equivalence of FOLFOX and CAPOX

Based on toxicity profile and antitumor activity, 5-FU is most com-

monly administered as a protracted venous infusion, either as monotherapy or in combination with other antineoplastics. Capecitabine is an orally administered prodrug of 5-FU, with equivalent antitumor activity and favorable tolerability as a single agent. The question naturally arises as to how capecitabine combinations compare with those utilizing a 5-FU backbone. In 2008, published reports provided guidance on this issue.

- Cassidy and colleagues conducted a study in which FOLFOX4 was compared with capecitabine plus oxaliplatin (CAPOX) in patients with previously untreated metastatic CRC.[27] After data supporting the benefit of bevacizumab was reported, the study was amended to include a second randomization to either bevacizumab or placebo (also see section III.B.2). Overall, 2,034 patients were randomized. The primary end point was PFS. Results showed no difference between the CAPOX and FOLFOX arms in PFS (HR 1.04; CI 0.93–1.16) or OS (HR 0.99; CI 0.88– 1.12).
- For patients with metastatic CRC who receive a 5-FU plus irinotecan regimen in the first-line setting, an oxaliplatin plus fluoropyrimidine combination is an appropriate subsequent treatment. Rothenberg et al[28] conducted a phase III trial in which patients who had previously received irinotecan were randomly assigned to treatment with FOLFOX4 or CAPOX. In 627 randomized patients, CAPOX was "non-inferior" to FOLFOX4, with an HR of 0.97 (CI 0.83–1.14) for the primary end point of PFS. Findings for median OS survival were similar.
- In 2008, Arkenau et al[29] presented a meta-analysis of six randomized phase II and III trials comparing oxaliplatin in combination with either capecitabine or infusional 5-FU. This analysis found a higher response rate with 5-FU–based regimens (odds ratio 0.85; 0.74–0.97, $P = .02$), but no difference in PFS or OS.

The studies comparing capecitabine to 5-FU identified differences in toxicity profiles. In general, CAPOX was associated with a greater frequency of hand-foot syndrome and diarrhea, whereas FOLFOX was associated with more neutropenia and febrile neutropenia. Overall, these data support anti-tumor equivalency of CAPOX and FOLFOX, perhaps with the exception of modestly lower response rates with CAPOX, and suggest that treatment selection should be based on patient clinical factors and preferences, including the out-of-pocket costs that are associated with treatment.

III-B. 2. Addition of Bevacizumab to Standard Chemotherapy

- A global trial funded by Roche enrolled 1,401 patients in a 2 × 2 factorial design to receive CAPOX vs. FOLFOX-4 with or without bevacizumab.[30] Saltz et al reported data in which the chemotherapy arms were pooled, and the focus was on comparing outcomes observed with bevacizumab to those with chemotherapy alone. The difference in median PFS favored the bevacizumab-containing regimens: 9.4 months compared with 8.0 months. While the PFS difference was less than 45 days, it was statistically significant with a P value of .002. The difference in median OS also favored bevacizumab-containing regimens at 21.3 vs. 19.9 months; this difference did not reach statistical significance ($P = .08$). A post-hoc analysis showed a trend toward a greater benefit when treatment was continued until disease progression rather than halted prior to that point. These data counterbalanced to some extent the level of enthusiasm toward bevacizumab use that arose from the findings in the initial pivotal trial.
- The TREE trial was a randomized phase II study conducted in two parts.[31] In the first portion, patients were randomized to FOLFOX6, bFOL (a bolus 5–FU-based oxaliplatin regimen), or CAPOX. In the second portion of the trial, bevacizumab was added to all three arms. As this was not a phase III study, the comparisons across arms are not adequately powered for statistical determinations and the authors refrained from that temptation. OS was best in the bevacizumab arms combined with FOLFOX6 (26 months vs. 19 months for FOLFOX6 alone) or CAPOX (25 months vs. 17 months with CAPOX alone). An explanation for the disparate findings regarding the incremental benefit attributable to the addition of bevacizumab is not readily apparent.

III-B. 3. Dual EGFR and VEGF Inhibition

Two important papers published in the past year looked at the potential value of using single- vs. double-antibody therapy (bevacizumab alone or combined with an EGFR-targeting antibody) plus combination chemotherapy.[32,33] The PACCE trial used panitumumab and the CAIRO 2 trial employed cetuximab. Both studies had the surprising outcome of showing a trend toward a detrimental effect in both activity and toxicity measures when the two classes of antibodies were delivered together in combination with chemotherapy.

- In the PACCE study,[32] the randomization was to FOLFOX with bevacizumab with or without panitumumab. The trial collected tissue but did not assign patients to therapy on the basis of *K-ras* mutation status. That aspect was examined retrospectively in a subset of enrolled subjects. There were 823 patients randomized. The PFS favored the bevacizumab arm at 11.4 months; OS was also better in this arm at 24.5 months. In the double-antibody arm, PFS was 10.0 months and OS was 19.4 months. Increased toxicity was also noted, mainly related to skin and gastrointestinal effects. The authors recommended against the use of double antibody modulation of FOLFOX as a consequence of these findings.
- In the CAIRO2 trial,[33] the control regimen was capecitabine plus oxaliplatin with bevacizumab (CB) with or without cetuximab (CBC). The trial enrolled 755 patients, and results were similar to those from the PACCE trial: The PFS favored the CB regimen (10.7 months) over the CBC regimen (9.4 months), while OS data have not yet been reported. Toxicity favored CB over CBC, with skin and gastrointestinal effects accounting for the difference. *K-ras* mutation analysis was available for 528 tumors, of which 40% manifested a mutation. Cetuximab-treated patients with mutations had a significantly shorter PFS than those with *K-ras* wild-type tumors (8.1 vs. 10.5 months).

These findings have led to modifications in the first-line and second-line US Intergroup trials, both of which contain a randomization to cetuximab in one or more arms, to include only patients with *K-ras* wild-type tumors.

III-B. 4. Bevacizumab Upon Progression While on First-Line Therapy

Controversy exists regarding the potential value of continuing

antiangiogenic therapy with bevacizumab beyond the time when patients manifest progression while on first-line therapy with a chemotherapy plus bevacizumab combination. Many feel that the unstable nature of the tumor genome that causes chemotherapy resistance is irrelevant to the genetically stable host vasculature targeted by bevacizumab. No prospective data exist to determine the benefit of continuing bevacizumab, but retrospective data are available from a Genentech-sponsored registry known as the BRiTE registry.[34] In this experience, data were collected from 1,953 patients managed at physician discretion. Patients were divided into three cohorts for the purpose of data analysis; no post-first-line therapy, no bevacizumab beyond progression, and bevacizumab post-progression. Median OS was 25.1 months, with medians of 12.6, 19.9, and 31.8 months according to the post-progression categories noted above. These data have led to the development of two ongoing prospective trials. The first one being conducted in the US, known as the S0600 study, is randomizing patients to cetuximab plus irinotecan with or without bevacizumab after progression. The second one is a Roche-sponsored trial—ML18147—being conducted in Europe that randomizes patients to second-line chemotherapy with or without bevacizumab after progression on a first-line bevacizumab-containing regimen. Caution in applying retrospectively obtained registry data to routine clinical practice is advised, in the absence of prospective data.

III-B. 5. Benefit in the Elderly Population

Several papers focused on the safety and efficacy of multiagent therapy in older patients.

- Folprecht et al[35] combined individual patient data from four first-line phase III trials that randomized nearly 2,700 patients to 5-FU with or without irinotecan, including 599 individuals (22%) ≥ 70 years of age. While the addition of irinotecan to 5-FU was associated with a statistically significant increase in grade ≥ 3 neutropenia, diarrhea, nausea, and vomiting, there was no difference in the incidence of these toxicities on the basis of age. No significant differences in response rate or OS based on age was noted, but older patients had a longer PFS (9.2 months) than did younger patients (8.2 months) ($P = .041$). Of note, 185 of these patients were ≥ 75 years old, making conclusions regarding that subgroup less robust.
- McKibbin et al[36] retrospectively examined the use of doublet chemotherapy in 520 consecutive patients treated at ten US community practices between 2003 and 2006. Of these patients, 56% were ≥ 65 years old. Younger patients (< 65 years old) received doublet therapy 84% of the time and older patients, 58% of the time ($P < .001$). Fewer older than younger patients received irinotecan (42% vs. 56%, $P = .002$), oxaliplatin (62% vs. 76%, $P < .001$) or bevacizumab (54% vs. 72%, $P < .001$). Of note, the median OS time for the older patients was 19 months compared with 24.5 months for younger patients. Adverse event data was less methodically captured in this group of patients as compared with those enrolled in prospective clinical trials due to the retrospective nature of the analysis. This experience reflects actual community practice and suggests that older patients are often treated less aggressively than younger patients in clinical practices.
- Bouchahda et al[37] examined the safety and efficacy of cetuximab with or without irinotecan in a retrospectively collected cohort of 56 heavily pretreated patients ≥70 years of age. Both efficacy (response rate, 21%) and toxicity seemed comparable to that reported in younger patients. Skin and gastrointestinal toxicities were most common, as expected.

IV. WHAT NEEDS TO BE DONE

IV-A. Comments on Research

In the last year, there has been an explosion of studies done to identify and validate prognostic or predictive biomarkers. Certainly the most interesting developments have revolved around the *K-ras* story and its negative predictive value for cetuximab or panitumumab response. However, a multitude of other biomarkers are now being explored and validated in a way that should elucidate their utility or lack of utility for influencing treatment decisions in individual patients. In metastatic disease, we continue to refine the interplay between surgery and medical therapy. Additionally, phase III trials and pooled analyses are helping us to discern the promise and pitfalls when multiple drugs are given together. These insights should help patients and physicians to optimize the use of the expanding palette of therapeutic options as current studies in progress mature.

To access information about active clinical trials in advanced and metastatic colorectal cancer in the National Cancer Institute data base, go to www.clinical trials.gov.

IV-B. Obstacles to Progress

Drug availability and cost have become major issues for managing colorectal cancer. Restricted availability of some agents and the impact of skyrocketing costs on fixed resources are two concerns creating ethical and fiscal dilemmas worldwide. In this regard, the development of predictive biomarkers may help in personalizing treatment selection and ultimately translate into a more cost-effective therapeutic approach.

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Disclosures of Potential Conflicts of Interest

Dr. Goldberg has served as a consultant for Amgen, Bristol-Myers Squibb, Genentech, ImClone, Abbott, AstraZeneca, Pfizer, sanofi-aventis, Myriad, ONI, and Poniard.

Dr. Meropol has served as a consultant to Genomic Health, Amgen, sanofi-aventis, AstraZeneca, and Genentech.

Dr. Tabernero has served on advisory boards for Amgen, Merck, Roche, sanofi-aventis, and ImClone.