New Approaches to Assessing and Treating Early-Stage Colon and Rectal Cancers: Cooperative Group Strategies for Assessing Optimal Approaches in Early-Stage Disease

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Abstract

The U.S. Gastrointestinal Intergroup (GI Intergroup), including the National Cancer Institute of Canada, has created a portfolio of clinical trials for patients with stage II and III colon and rectal cancer, integrating therapeutic strategies from recent advanced disease trials. Fluoropyrimidine-based combination therapy for metastatic disease, with either irinotecan or oxaliplatin plus bevacizumab, has resulted in significant improvement in response and disease-free and overall survival. Cetuximab and irinotecan have produced intriguing response and progression-free survival data from randomized phase II trials. Although patients with stage II and III rectal cancer are uniformly included in individual clinical trials, the GI Intergroup conducts separate trials in patients with stage II and III colon cancer, with the exception of the National Surgical Adjuvant Breast and Bowel Project (NSABP), which continues to merge both stages in their statistical designs. The U.S. chemotherapy platform for adjuvant therapy clinical trials is based on the positive adjuvant data from NSABP C-07 [FLOX with bolus 5-fluorouracil (5-FU)] and the MOSAIC trial (FOLFOX with infusional 5-FU). Three irinotecan-based adjuvant trials (one U.S. and two European) did not reach designated statistical end points. In addition, the GI Intergroup has consistently integrated molecular biological and other laboratory projects as important components of past and current trials. NSABP has recently completed accrual of patients to C-08, which is evaluating FOLFOX with or without bevacizumab in stage II/III colon cancer. E5202, the largest U.S. stage II colon cancer trial, determines patient risk by the initial evaluation of tumor 18q loss of heterozygosity and microsatellite instability status. Low-risk patients are observed, whereas high-risk patients are randomized to FOLFOX with or without bevacizumab. N0147 evaluates FOLFOX with or without cetuximab in patients with stage III disease. Two large rectal cancer trials have begun to accrue patients. NSABP R-04 compares neoadjuvant radiation with either continuous infusion 5-FU with or without oxaliplatin versus capecitabine with or without oxaliplatin. E5204 is the adjuvant comparison of FOLFOX with or without bevacizumab and is also available to NSABP R-04 patients.

The unprecedented evolution of colorectal cancer treatments has introduced significant challenges in clinical trial design. The integration of multidrug combinations, including chemotherapy agents and the new biologics, the variety of treatment schedules and sequences, and the quest to unmask the human biological links to these treatment strategies have been a driving force during the past decade. The development of irinotecan, oxaliplatin, capcitabine, bevacizumab, cetuximab, and panitumumab, combined with the controversy about the optimal fluoropyrimidine regimen (i.e., oral versus i.v. infusion versus i.v. bolus), has fueled the momentum to create a continuum of treatment options across multiple lines of therapy for advanced colorectal cancer. Historically, advanced disease response data have justified the inclusion of regimens in the adjuvant setting. Most recently, however, the principle of adjuvant design strategy has produced imperfect results. The U.S. Gastrointestinal Intergroup (GI Intergroup), which includes the National Cancer Institute of Canada, has worked to produce a new portfolio of adjuvant clinical trials in both colon and rectal cancer that borrows from the lessons of the recent past and infuses laboratory-based hypotheses as a critical component. A discussion of these trials forms the basis of this brief review.

Colon Cancer Adjuvant Trials

Beginning ~ 6 years ago, the design of new adjuvant studies in both colon and rectal cancer focused on the publication of survival benefit of irinotecan combination therapy for first-line advanced disease in patients with colorectal cancer. Evolving
data that focused on oxaliplatin-containing regimens in the advanced disease setting were also of interest. Over time, however, a mid-course correction in strategy was necessitated, as biological agent advanced disease data were reported, toxicities were clarified, and the more recently completed adjuvant data were presented—at least as preliminary reports. In addition, infusion 5-fluorouracil (5-FU)-based combinations and the integration of oral agents were favored over an i.v. bolus approach, primarily based on toxicity concerns.

The publication of U.S. first-line advanced disease data showing the superiority of the IFL regimen (irinotecan, bolus 5-FU, and leucovorin), compared with the Mayo Clinic bolus 5-FU and leucovorin regimen, and European data showing the benefits of infusion 5-FU and irinotecan schedules, compared with infusion 5-FU and leucovorin, provided the justification necessary to develop large irinotecan-based adjuvant clinical trials in both the United States and Europe (1, 2). The Europeans maintained that infusion 5-FU schedules were safer and probably more efficacious than bolus combinations. In North America, interest focused on the convenience of bolus regimens and avoidance of the complexities of infusion pumps. Unfortunately, neither approach confirmed the expected efficacy benefits of irinotecan combination therapy in patients with resected colon cancer, raising the concern that perhaps the improved response and progression-free and overall survival shown in advanced disease trials imperfectly predicted the survival benefit with adjuvant therapy (3–5).

CALGB 89803, a GI Intergroup adjuvant stage III colon cancer trial, compared IFL (irinotecan 125 mg/m², leucovorin 20 mg/m², 5-FU bolus 500 mg/m² weekly × 4 every 6 weeks for five cycles) with the Roswell Park leucovorin/5-FU regimen (leucovorin 500 mg/m², 5-FU bolus 500 mg/m² weekly for 6 weeks every 8 weeks for four cycles; ref. 3). The trial accrued 1,263 patients. After 4.8 years of follow-up, no overall survival benefit was found with IFL (P = 0.74), and the regimen resulted in significantly more febrile neutropenia and higher mortality during treatment (2.8% versus 1%, respectively; P = 0.008). Coupled with advanced disease IFL data, CALGB 89803 helped to solidify a growing consensus that IFL was not an appropriate regimen for routine use.

PETACC-3 (V307), another irinotecan adjuvant trial, included patients with stage II and III colon cancer who received either irinotecan, 5-FU, and leucovorin (irinotecan 180 mg/m²/day 1), leucovorin 200 mg/m², bolus 5-FU 400 mg/m², and infusional 5-FU 600 mg/m² (days 1 and 2) every 2 weeks for 12 cycles or the LV/5-FU2 regimen without irinotecan (4). As per the stated protocol design, the 3-year disease-free survival was not statistically different (P = 0.91). When risk was adjusted for tumor (T) and node (N) status in a retrospective analysis, 3-year disease-free survival favored the FOLFIRI regimen. These data emphasize the importance of risk stratification using the T and N system in adjuvant clinical trials, given the differences in survival among the subsets of patients with stage II and III colon cancer (6).

A third trial, ACCORD-02, also compared FOLFIRI to the LV/5-FU2 regimen in 400 high-risk patients. No statistically significant difference was found between regimens (5).

In contrast to the disappointing irinotecan adjuvant trial results, two recent oxaliplatin-based combination trials showed a significant difference in disease-free survival compared with the 5-FU and leucovorin regimens (7–9). The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial randomized 2,246 patients with stage II and III colon cancer to either FOLFOX4 [oxaliplatin 85 mg/m² (day 1), leucovorin 200 mg/m², bolus 5-FU 400 mg/m², followed by a 22-h infusion of 5-FU at a dose of 600 mg/m² on days 1 and 2, every 14 days, for 12 cycles] or the same regimen of 5-FU and leucovorin without oxaliplatin (LV/5-FU2; refs. 7, 8). FOLFOX4 produced a statistically significant disease-free survival advantage at both 3 and 4 years. The difference between the two arms at 4 years in patients with stage III N1, III N2, and II disease was 7.2%, 11.5%, and 5.4%, respectively. Of note, patients at highest risk obtained the greatest benefit from FOLFOX4. The incidence of grade 3 peripheral neuropathy was 12.4% in patients receiving FOLFOX.

National Surgical Adjuvant Breast and Bowel Project (NSABP) has reported the initial results of C-07, which included 2,400 patients with stage II and III disease randomized to either the Roswell Park 5-FU/LV regimen or the same 5-FU bolus therapy with the addition of oxaliplatin 85 mg/m² administered on weeks 1, 3, and 5 every 8 weeks for three cycles (FLOX; ref. 9). Three-year disease-free survival was statistically superior to 5-FU/LV (76.5% versus 71.6%, respectively; difference of 4.9%). These results are remarkably similar to the 3-year disease-free survival data in MOSAIC. The reduced total exposure of oxaliplatin in the FLOX regimen in C-07, compared with that in MOSAIC (cumulative dose of 765 versus 1,020 mg/m², respectively), resulted in significantly fewer cases of grade 3 neuropathy (8%). In C-07, 38% of patients receiving FLOX reported grade 3/4 diarrhea, compared with 10.8% receiving FOLFOX4 in MOSAIC. In C-07, 32.3% of patients receiving the Roswell Park 5-FU/LV regimen reported grade 3/4 diarrhea, compared with 6.7% of patients receiving LV/5-FU2 in MOSAIC.

The current GI Intergroup adjuvant colon cancer strategy embraces a number of concepts: (a) an overall goal to move closer to developing individual patient treatment strategies; (b) the integration of retrospective lab data to develop prospective hypothesis-driven translational research projects; (c) the incorporation of disease-free survival as a primary efficacy end point based on a recent pooled analysis showing high correlation between disease-free and overall survival in patients with stage III colon cancer (10); (d) the incorporation of oxaliplatin-based rather than irinotecan-based regimens as the platform chemotherapy in adjuvant patients; (e) the integration of bevacizumab with combination chemotherapy based on phase III first-line and second-line data in patients with advanced colorectal cancer receiving bevacizumab combinations (11, 12); (f) the evaluation of cetuximab combinations in the adjuvant setting in patients with stage III disease based on randomized phase II data in patients with advanced disease receiving second-line and third-line therapy (13); and (g) the design of separate trials in patients with stage II and III colon cancer (although NSABP continues to combine stage II and III patients).

The current portfolio of trials includes NSABP C-08, which recently completed accrual. In C-08, patients with stage II and III colon cancer are randomized to receive either FOLFOX or FOLFOX plus bevacizumab; of note, bevacizumab will be continued for an additional 12 cycles (6 months) after completion of an initial 6 months of FOLFOX and bevacizumab.
NCCTG 0147 was designed initially as a three-arm trial in which patients with stage III colon cancer were randomized to receive FOLFOX or FOLFIRI (both for 24 weeks) or 12 weeks of FOLFOX followed by 12 weeks of FOLFIRI. The protocol was extensively revised, however, when it became clear that the irinotecan adjuvant trials had not reached their statistical end points. Growing interest in the evaluation of biological therapies in adjuvant trials also played a role in the revision. In 2005, N0147 was redesigned as a two-arm trial to accrue 2,400 patients with stage III colon cancer. Patients are randomized to receive the modified FOLFOX6 regimen with or without cetuximab. Both regimens are administered for 6 months (Fig. 1).

Analyses conducted by Cancer Care Ontario and the American Society of Clinical Oncology have shown that the routine use of adjuvant chemotherapy in most patients with stage II colon cancer is not warranted because the difference in outcome, compared with observation, represents only a few percentage points (14, 15). Furthermore, most clinical trials that have included patients with stage II colon cancer are too small to adequately address the benefits of adjuvant therapy in this population. Retrospective data, including analyses by the cooperative groups, suggest that molecular prognostic factors may be helpful in identifying patients at greatest risk of relapse and perhaps those who are most likely to benefit from adjuvant therapy. For example, patients without 18q loss of heterozygosity (LOH) and those whose tumors show microsatellite instability (MSI) with the transforming growth factor-β1 receptor II mutation seem to have the best prognosis (16). E5202 is the largest stage II colon cancer trial conducted by the GI Intergroup and the first in which patients with colon cancer are selected prospectively for adjuvant therapy based on molecular marker status (18q LOH and MSI). Patients (n = 3,600) will be stratified by disease stage (IIA or IIB), microsatellite status [microsatellite stability (MSS) versus MSI], and 18q LOH status (Fig. 2). Low-risk patients, defined as those with MSS or MSI-L with retention of 18q alleles or MSI-H, will be observed, with an expected survival of nearly 90%. High-risk patients, defined as those with MSS and 18q LOH or with MSI-L and 18q LOH, will be randomized to regimens identical to those in NSABP C-08 (i.e., modified FOLFOX6 with or without bevacizumab, with bevacizumab continued for an additional 6 months on completion of the combination with FOLFOX).

One of the most important features of the current GI Intergroup colon cancer portfolio is the development of extensive tumor banks. These tumor banks will contribute to the goal of identifying other prognostic and predictive factors in the future that can be linked to the well-documented clinical data available from the above-mentioned trials. One example of future laboratory-based analysis is the creation of gene signatures from DNA chip analyses (DNA microarrays), with the hope of defining low-risk and high-risk groups as well as the probability of distant relapse. For example, a recently reported genetic signature of relapse in patients with stage II colorectal cancer using a disease-specific colorectal array showed a significant survival difference based on a gene signature definition of poor and good prognosis (17). NSABP recently reported the relationship between gene expression and recurrence in stage II/III colon cancer using a quantitative reverse transcriptase-PCR assay of 757 genes in paraffin-embedded tissue (18). In this analysis, the investigators noted a relationship between gene expression and recurrence-free interval that was similar in patients with stage II and III disease in 143 of the 148 genes found to be significant.

Rectal Cancer Clinical Trials

The established goals of rectal cancer treatment include improvement in local control and long-term survival with preservation of anal sphincter, bladder, and sexual function while maintaining or improving quality of life. An additional goal has emerged as a focus of GI Intergroup clinical trials to include the development of prognostic and predictive markers. A consistent challenge has centered not only on these important goals but also on the accurate reporting of surgical technique and precise pathologic staging. Critical surgical management issues include obtaining a total mesorectal excision, autonomic nerve and sphincter preservation, circumferential and distal resection margin evaluation, restoration of bowel continuity, and enhancement of postoperative quality of life (19).

As in colon cancer, pathologic prognostic factors have been identified in rectal cancer that could influence survival and risk of local recurrence. For example, in GI Intergroup 0114,
a phase III postoperative adjuvant chemoradiation trial of nearly 1,700 patients with stage II and III rectal cancer, which evaluates chemotherapy and chemoradiation with bolus 5-FU with or without leucovorin and/or levalmisole, noted significant survival differences determined by the number of lymph nodes resected and examined (20). In patients who had 14 or more lymph nodes sampled, survival was 82%, compared with only 68% in those with 0 to 4 resected nodes. This trial also defined two risk groups based on T and N staging. Seven-year survival and local recurrence were significantly more favorable in patients with low-risk (T1, N0, or T2 N1a) disease than those with high-risk (T3 N0, or T4 any) disease, respectively (P < 0.0001; 9% versus 18%, respectively (P < 0.0001)). Of note, neither of the two most recent postoperative GI Intergroup trials evaluating chemotherapy and chemoradiation (INT0114 and INT0144) has shown a relapse-free or overall survival advantage favoring any 5-FU schedule, whether administered as bolus or infusion therapy or administered with leucovorin and/or levalmisole (20, 21).

Preoperative chemoradiation in patients with stage II and III rectal cancer has clearly emerged as the preferred approach, with goals of improving the number of patients obtaining a complete response and decreased local recurrence rate; increasing both the resectability rate and the ability to perform sphincter-sparing surgery; downstaging based on clinical T and N status; and reducing the morbidity of combined modality therapy. As one example, the German Rectal Cancer Group compared neoadjuvant versus adjuvant chemotherapy and radiation, showing improved local recurrence (6% versus 13%; P = 0.0006) and twice the number of sphincter-sparing procedures with the neoadjuvant approach; however, 5-year disease-free and overall survival were comparable (22). Unfortunately, neither NASBP nor GI Intergroup was able to accrual to preoperative versus postoperative therapy trials.

NASBP R-03 data from the 253 eligible patients who did accrue suggested a nonsignificant trend toward improvement at 3 years favoring preoperative versus postoperative therapy [overall survival, 85% versus 78%, respectively (P = 0.15); disease-free survival, 70% versus 65%, respectively (P = 0.40); and relapse-free survival, 77% versus 70%, respectively (P = 0.22); ref. 23].

In 2001, with the recognition that both preoperative and postoperative adjuvant strategies were used in the United States, the GI Intergroup designed E3201. The trial offered a “dealers’ choice,” allowing patients and physicians to select either preoperative chemotherapy and radiation or postoperative combined modality therapy. Because both irinotecan and oxaliplatin at the time were incorporated in adjuvant colon cancer clinical trials, E3201 also planned to compare the effectiveness of combination therapy in a three-arm design evaluating FOLFOX versus FOLFIRI versus 5-FU/LV. Subsequently, with the emergence of colon cancer irinotecan data, an interest in biological treatment combinations, and a growing preference for preoperative chemoradiation, E3201 was terminated. Follow-up data in 123 patients provided important comparative toxicity information, showing that FOLFOX can be safely administered to patients with rectal cancer following chemoradiation (24).

Recent phase I/II neoadjuvant rectal cancer trials have focused on the role of combination chemotherapy regimens with radiation as an effort to further improve complete response before surgical resection. CALGB 89901 evaluated continuous infusion 5-FU, weekly oxaliplatin, and radiation in patients with T3 or T4 rectal cancer showing a complete pathologic response of 25% (25). Eastern Cooperative Oncology Group designed a phase I oxaliplatin dose-escalation trial, administering every other week oxaliplatin with continuous infusion 5-FU and radiation; the rate of microscopic residual disease was found to be 50%, with a pathologic complete response of 30% (26). Preoperative radiation, oxaliplatin, and capecitabine resulted in significant downstaging of patients in a European trial (27). In addition, a small phase I rectal cancer trial suggested an antivascular and antitumor effect with the addition of the monoclonal antibody bevacizumab (28).
The current GI Intergroup strategy embraces concepts to improve the efficacy of both neoadjuvant combined chemoradiation and adjuvant chemotherapy. NASBP R-04 was recently amended to include oxaliplatin in a $2 \times 2$ design (Fig. 3). This randomized phase III trial of >1,600 patients will compare radiation with infusional 5-FU with or without oxaliplatin and capecitabine with or without oxaliplatin. The new GI Intergroup adjuvant rectal trial E5204 will help to determine whether combination postoperative systemic therapy can further improve disease-free and overall survival (Fig. 4). NASBP R-04 patients have been encouraged to also enroll in E5204, which is a two-arm randomized trial of modified FOLFOX with or without bevacizumab administered for 12 cycles. These large trials will provide an unparalleled database with which to address a host of questions. For example, detailed analysis of acute and long-term sequelae of combined modality multidrug regimens in patients with rectal cancer will be undertaken, which will include the Patient Bowel Function questionnaire and the FACT-Diarrhea subscale evaluation over time. Pathology and surgical review is an essential component of these trials to better address the percentage of patients receiving total mesorectal resection and to assess clinical and pathologic factors as a measure of quality of care and prognostic association. The future study of evolving potential prognostic and predictive tumor-specific markers will be achievable as a result of the prospective collection of tumor blocks from patients who enter these two rectal cancer trials.

The cooperative groups are also accruing patients to phase II trials to provide additional toxicity data and potential regimens for future phase III randomized trials in patients with rectal cancer. For example, RTOG 0247, a randomized phase II trial evaluating capecitabine administered 5 days per week and weekly oxaliplatin plus radiation administered before surgery followed by nine cycles of postoperative FOLFOX chemotherapy, has nearly completed accrual. The second arm substitutes irinotecan for oxaliplatin and is also administered on a weekly schedule. Another phase II trial, E3204, combines capecitabine administered 5 days per week plus weekly oxaliplatin and every other week bevacizumab with radiation; postoperative patients receive 12 cycles of FOLFOX and bevacizumab.

Numerous rectal cancer treatment questions remain unanswered. For example, are there subsets of patients who may not require radiation therapy? Gunderson et al. (29) have evaluated the effect of T and N stage and treatment on survival and relapse of rectal cancer as a pooled analysis. The authors observed that patients with intermediate-risk rectal cancer ($T_{1-2}N_0$, $T_3N_0$) seem to derive no additional benefit from radiation in combination with surgery and chemotherapy, compared with patients treated with surgery and chemotherapy without radiation. In Europe, investigators have studied short-course radiation schedules, which, in contrast to prolonged-course radiation, raises questions about the importance of the downstaging of rectal cancer and surgical resectability as well as the effect of pathologic complete response on survival (30, 31). It is believed that the best opportunity to improve survival in patients with rectal cancer will require continued focus on adjuvant chemotherapy strategies, while at the same time pursuing detailed assessment of both acute and chronic toxicities. Additionally, if treatment strategies are to be successful in patients with rectal cancer, enhanced understanding of tumor biology is essential.

### Conclusion

In summary, the GI Intergroup has recently developed a portfolio of high-profile, high-priority trials asking state-of-the-art questions. The National Cancer Institute/Centers for Medicare and Medicaid Services has designated these and other GI Intergroup trials as clinical studies of the highest importance in the United States. As such, Centers for Medicare and Medicaid Services has offered guaranteed reimbursement for Medicare patients who participate. The success of these trials requires an urgent need for commitment to the cooperative group mission on the part of the groups’ community and academic members. The advances in efficacy that may emerge from these clinical trials will be enhanced by the associated collection of human tumors. It is only through this quest to link efficacy data with human tumor biology that we will truly come closer to prescribing individualized treatment approaches.

### References

Discussion: Issues in Adjuvant Therapy for Early-Stage Disease

Dr. Axel Grothey: The first decision is whether to administer adjuvant therapy. If yes, the second decision is determining which adjuvant therapy to use. Once you make a decision and show that the high-risk stage II patient benefits to the same extent as the stage III patient, why differentiate? Nonetheless, there are nuances, and its never a black and white decision. I would pay great attention to the point at which neurotoxicity occurs.

Dr. Daniel Haller: One of the reasons we use cetuximab is because of the late toxicities of combining radiation and bevacizumab, which are both antiangiogenic. Many of the complications from radiotherapy, including neuropathies, are associated with blood vessel (not nerve) damage. Is there any concern about giving a full 12 months of bevacizumab after radiation therapy?

Dr. Christopher Willett: No neurological toxicities were observed in the bevacizumab trial, and the cetuximab trial has not reported any problems. I believe that oxaliplatin was also used in the trial.

Dr. Haller: I'm concerned about the monitoring of long-term toxicities (e.g., continence, urgency, etc.).

Dr. Willett: In fairness, the cetuximab and bevacizumab trials are preliminary phase I/II studies and will need further follow up. The German trial is a more mature study with large patient numbers. The late effects were well analyzed and consistent with what many have observed.

Dr. Lee Rosen: Yes, but after 10 years of patients having been treated with vascular endothelial growth factor inhibitors it for metastatic diseases clear that we should not be cavalier about their use.

Dr. Haller: As was discussed within the context of stage II disease, the routine use of unproven drugs should not be recommended.

Dr. Willett: Oftentimes in rectal cancers where a complete clinical response is achieved, reepithelialization at the site of the tumor will occur after preoperative radiation with fluoropyrimidine or a cytotoxic agent of some sort, even 7-9 weeks after the last administration. With bevacizumab, you are left with a crater in the specimen.

Dr. Robert Beart: It seems that there would be substantial economic and logistic benefits for being able to administer a short treatment course and that we should be working toward this goal.

Dr. Michael Stamos: Such treatment could be used in patients who don't require tumor shrinkage to get the desired results.

Dr. Beart: Radiation therapy will alter little in patients who are in the hands of an experienced surgeon. When I see 30% or 40% differences in salvage rates, plus a population in which 30% abdominoperitoneal resections are currently being performed, it's difficult to understand.

Dr. Willett: The Polish trial may stimulate further evaluation, but perhaps not in the next few years. The Swedish trial enrolled about 1,400 to 1,600 patients, so it was well powered, and a statistical advantage in local control and survival to surgery alone was demonstrated.

Dr. Grothey: With regard to systemic relapse risk, we would like to treat patients as early as possible. Patients eventually die of systemic disease, not necessarily of local relapse. This strategy implies the use of novel agents and better risk assessment, so my focus would be to integrate bevacizumab or cetuximab as soon as possible; however, this is not an option with a 5 \times 5 \text{ Gy} schedule followed by surgery followed by a long interval before novel drugs can be used. If our goal is better systemic control, we should integrate these agents early. In the context of long-term radiation, our future plan should probably not be a 5 \times 5 \text{ Gy} schedule, but rather developing a strategy to limit systemic risk of relapse.

Dr. Haller: In our trial, the vast majority of patients treated with adjuvant therapy received 4 months of chemotherapy (CAPOX) plus cetuximab before surgery.

Dr. Willett: Late toxicity is an issue with that fractionation.

Dr. Beart: I thought that starting chemotherapy early in patients with recurrent disease does not necessarily prolong life. Early treatment subjects patients to an increased length of toxicity, so we would wait until they became symptomatic to start recurrent therapy.

Dr. Haller: I agree that not every patient needs to be treated urgently; however, if you wait until patients with metastatic disease are symptomatic, it's too late.

Dr. Grothey: Rather than waiting until systemic metastasis is established, it might be better to treat early when tumor volume is at its lowest.

Dr. Rosen: We may not be affecting overall survival, but quality of life, number of toxicities, and other things that are so important to patients must obviously be balanced with issues of economics.

Dr. Stamos: The duration of time between completion of radiation and surgery has historically been 6 weeks, but published data show that you can wait ≥12 weeks with no increased surgical morbidity. In conjunction with UCSF, we are investigating additional chemotherapy in the interval between...
radiation and surgery, or perhaps giving chemotherapy up front followed by radiation.

**Dr. Rosen:** How certain are we that biologics really need to be in a separate category from cytotoxics?

**Dr. Grothey:** It also shows us that the caveat and the kind of question mark we put around biologics should have applied to chemoradiation therapies in the first place. We all thought that IFL would be better as adjuvant therapy than 5FU, but the opposite is true. In the end, it shows us that we shouldn't let our guard down.

**Dr. Rosen:** We need to be mindful of drug overuse, especially in patients in whom we are beginning to question whether adjuvant therapy is appropriate at all, let alone treating them with a variety of different drugs.

**Dr. Grothey:** I think that these novel drugs should not be used outside of clinical trials because we can harm patients in the adjuvant setting. There is the long-term risk of, let's say, bevacizumab-related toxicities. Its a different situation if you have 75% or 80% of patients who are cured anyway vs. a patient with metastatic disease whose median survival is about 2.5 years.

**Dr. Rosen:** What about length of adjuvant therapy?

**Dr. Grothey:** In the MOSAIC trial, dose intensity was about 81%, so the median number of oxaliplatin cycles was 10. Increasing evidence suggests that we can probably get by with fewer cycles.

**Dr. Rosen:** What are the main issues relating to complications or surgeries in patients who are treated adjuvantly?

**Dr. Beart:** We recently had an article accepted that showed several late complications, including an anastomotic leakage at 5 months after a low anterior anastomosis, and another patient developing a rectal/vaginal fistula 5 or 6 months after surgery on adjuvant bevacizumab.

**Dr. Bilchik:** A group at M.D. Anderson believes that bevacizumab may be protective in combination with oxaliplatin in reducing toxicity. We haven’t seen many complications, with the exception of some spontaneous perforations in patients with bulky ovarian cancers.

**Dr. Rosen:** In the context of current therapy, not future clinical trial design, should anything other than 6 months of therapy be advocated in patients that we are going to treat?

**Dr. Grothey:** I would consider FOLFOX, which is most widely used, and discontinue oxaliplatin as early as necessary to prevent severe neurotoxicity. I haven’t pushed for 12 cycles of therapy in cases where the last two cycles were difficult to administer.

**Dr. Haller:** I think that the data showing resolution of neurotoxicity is grossly underreported. I would be perfectly happy with six cycles of FOLFOX and six more cycles of LV5-FU2. Even if the XELOX trial has positive results, I would feel the same way, but neuropathy is a gift that keeps on giving in some patients.

**Dr. Al Benson:** Neurotoxicity can worsen after you stop treatment, which is a critical message.

**Dr. Haller:** With regard to FOLFOX in stage II disease, some oxaliplatin (rather than none) should be administered. We should differentiate between the ideal protocol dose, which nobody receives, and the 80% dose, which is actually administered. A dose of less than 80% would probably be required to avoid large numbers of grade II and III toxicities.

**Dr. Grothey:** In the original MOSAIC trial, 6 of 12 patients who had grade III or IV neurotoxicity 1 year after discontinuation of therapy developed grade III neurotoxicity after discontinuation of oxaliplatin. Late onset neurotoxicity is greatly underappreciated, but common in clinical practice.

**Dr. Haller:** The OPTIMOX I trial, in which patients with metastatic disease received six cycles of FOLFOX followed by fluoropyrimidines alone vs. continuous FOLFOX dosing, supports this idea. No difference was reported in response rate, progression-free survival, or overall survival. I start questioning at six cycles.
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