ABSTRACT

The development of new chemotherapies and biologic therapies has changed the way medical oncologists view the treatment of colorectal cancer because larger percentages of patients are responding to these new therapies. As a first-line therapy, oxaliplatin- or irinotecan-based regimens (5-fluorouracil [5-FU], leucovorin, and oxaliplatin [FOLFOX] or folinic acid, 5-FU, and irinotecan [FOLFIRI]) are the most efficacious regimens. Adding a biologic agent to first-line chemotherapy has the potential to augment the efficacy of cytotoxic treatments. After first-line FOLFOX, FOLFIRI is a good second-line option, and vice versa. The use of second- and third-line agents has been shown to improve patient survival, and sequential use of these agents has the potential to limit toxicity and hence treatment failure. Future treatment paradigms will likely bundle and sequence therapies according to patient characteristics, thus all patients in which treatment is conducted with clear palliative intent receive maximum exposure to the available agents, with the goal to prolong their life and maintain their quality of life as long as possible. A certain subset of patients with metastatic disease will be considered candidates for a curative approach by downsizing initially unresectable metastases followed by metastasectomy. In contrast to the truly palliative setting, the choice of therapy in these patients will try to maximize response rates rather than delay tumor progression.


CURRENT BEST-PRACTICE CHEMOTHERAPY

Infusional 5-FU and leucovorin (LV) in combination with irinotecan (folinic acid, 5-FU, and irinote-
can [FOLFIRI regimen] or oxaliplatin (5-FU, LV, and oxaliplatin [FOLFOX] regimen) has become the standard of care first-line treatment for colorectal cancer. Phase III trials of irinotecan- and oxaliplatin-containing therapies demonstrated that both agents improved response rates and progression-free survival rates compared to 5-FU/LV alone, with less consistent effects on overall survival rates because overall survival is greatly affected by subsequent lines of therapy.

A randomized phase III study compared first-line FOLFOX followed by second-line FOLFIRI with first-line FOLFIRI followed by second-line FOLFOX. This study showed that 21% of patients who received first-line FOLFOX were able to receive liver resection compared to 9% of patients who received first-line FOLFIRI. However, this difference may reflect bias because surgeons may be more receptive to candidates treated with neoadjuvant FOLFOX. A higher response rate associated with the regimen used.

Despite observed treatment differences with initial therapies, it is important that patients are exposed to second- and third-line agents because exposure to 3 lines of chemotherapy is associated with increased survival. A treatment paradigm that provides sequential exposure to cytotoxic agents may help maximize survival in the palliative setting.

**BIOLOGIC THERAPY**

**EPIDERMAL GROWTH FACTOR**

Epidermal growth factor (EGF) became a target for cancer therapies after immunohistochemistry studies showed that more than 80% of tumors overexpress EGF receptors. EGF receptor signaling has been associated with tumor cell proliferation, and blocking of this pathway has been associated with improved outcomes in patients with other kinds of cancer.

Cetuximab is a chimeric monoclonal antibody that is composed of human and mouse protein and that binds to the extracellular domain of the human EGF receptor. Cetuximab has mostly been studied as salvage therapy in patients who were pretreated with irinotecan. If cross-trial comparison is allowed, phase II studies showed that cetuximab monotherapy has second-line efficacy that is similar to FOLFOX after failure of irinotecan combined with 5-FU/LV (IFL). Cunningham et al showed that 11% of patients receiving cetuximab single agent and 23% of patients on cetuximab plus irinotecan as salvage therapy had a clinically relevant treatment response. EGF expression level as determined by immunohistochemistry was not

**SUMMARY**

FOLFOX has so far been the most widely studied regimen as neoadjuvant first-line therapy in metastatic colorectal cancer. In the absence of well-conducted, prospectively randomized studies on neoadjuvant therapy, it is unclear if FOLFOX or FOLFIRI is the superior regimen in this setting. The ability of a neoadjuvant treatment to effectively downsize metastasis for secondary resection is mainly dependent on the response rate associated with the regimen used.

Regardless of observed treatment differences with initial therapies, it is important that patients are exposed to second- and third-line agents because exposure to 3 lines of chemotherapy is associated with increased survival. A treatment paradigm that provides sequential exposure to cytotoxic agents may help maximize survival in the palliative setting.
a predictor for treatment response. However, the emergence of an acne-like rash was a predictor. \(^{13,14}\) Rash severity correlated with treatment response and survival for colorectal cancer and tumors at other sites.\(^{15}\)

Several clinical trials have examined front-line regimens of combined cetuximab and chemotherapy. The most recent trial was a European international phase II study that showed that 72% of patients who received combined cetuximab and FOLFOX-4 responded to therapy with a disease control rate of 95% and a time to progression of 10.2 months.\(^{16}\) Similar results were found among 3 other studies of cetuximab combined with front-line chemotherapies, in which the addition of cetuximab was associated with increased overall response rates.\(^{17-19}\)

**ANTIANGIOGENESIS**

Blood vessel structure differs between tumor tissue and normal tissue (Figure 2). Normal blood vessels are well organized, have well-aligned endothelial cells, and do not require the presence of survival factor for their integrity. However, tumor blood vessels are contorted, have misaligned endothelial layers, and have holes in their walls that create a higher interstitial pressure, which inhibits the delivery of chemotherapy into the tumor.\(^{20}\) In addition, immature tumor blood vessels need the constant presence of vascular endothelial growth factor (VEGF). VEGF is key in the angiogenic process, driving endothelial cell migration, proliferation, apoptosis, and vascular permeability.\(^{21}\) The VEGF family is composed of a number of different ligands that bind to receptors on the surface of endothelial cells.\(^{22}\) Of these ligands, VEGF-A plays the largest role in tumor angiogenesis by binding to VEGF receptor 2. Preclinical studies have shown that VEGF overexpression increases the number of blood vessels.\(^{23}\) However, microvessel density was reduced in the presence of a VEGF inhibitor, allowing increased penetration of chemotherapeutic agents (Figure 3).\(^{21}\)

Bevacizumab is a humanized monoclonal antibody that targets VEGF-A, which is the key ligand to activate VEGF receptor 2 (KDR). It has a half-life of approximately 3 weeks, which has implications for surgery because angiogenesis is necessary for wound repair.\(^{24}\) A phase III trial in previously untreated patients with metastatic colorectal cancer showed that patients receiving IFL and bevacizumab had increased median progression-free survival time by 4.5 months compared to patients receiving IFL and placebo \((P < .0001).^{25}\) The overall response rate was increased by 10% in the group receiving bevacizumab compared to the placebo group \((P < .005).\) Figure 4 shows the survival curves for the 2 patient groups, in which separation of the curves was achieved early and was sustained.

Analysis of a third arm of this phase III study, which contained bolus 5-FU/LV in combination with bevacizumab, suggested that bevacizumab added more benefit to 5-FU and LV than irinotecan.\(^{26}\) Likewise, data of a second-line phase III trial in bevacizumab-naïve patients who had progressed on irinotecan-based first-line therapy showed that the addition of bevacizumab had increased median progression-free survival time by 4.5 months compared to patients receiving irinotecan and placebo \((P < .0001).^{27}\)
Bevacizumab to FOLFOX therapy increased overall survival, increased progression-free survival, and improved the overall response rate by approximately 10%. Bevacizumab monotherapy was shown to be inferior to FOLFOX monotherapy in this study.27

The adverse events associated with bevacizumab therapy in phase III study included gastrointestinal (GI) perforation and grade 3 hypertension. Hypertension appears to be a class effect of VEGF inhibitors that is manageable with antihypertensive therapy. Rates of grade 3 or 4 bleeding, venous thromboembolism, and grade 3 proteinuria were not significantly different between treatment groups.28 To get a better understanding of potential clinical risk factors for rare, serious side effects such as GI perforations, the manufacturer of bevacizumab has started a registry to follow 1986 patients who are being treated with combinations of bevacizumab and chemotherapies.29 To date, the rate of GI perforations in these patients has remained low at 1.5% to 2%, and investigators are trying to determine clinical characteristics that may help identify patients who are at risk for these perforations.

Patients receiving bevacizumab also appear to be at increased risk of arterial thromboembolic/thrombotic events (ATEs). A pooled analysis of 5 trials that enrolled approximately 1700 patients with 3 different tumor types (breast, lung, and colorectal) showed a 2-fold increased risk for an arterial event in patients receiving bevacizumab. For patients older than 65 years or those with a history of arterial thrombosis, the risk is higher than 2-fold and climbs to almost 18% in patients who are 65 years of age and have a history of ATEs.29 However, withholding bevacizumab treatment from high-risk patients may not be a prudent option because further analysis of the data demonstrated that bevacizumab treatment in patients older than 65 years who had a history of arterial thrombosis reduced their risk of death and tumor progression to the same magnitude as in the general patient population of the study.29 Therefore, high-risk patients should be informed of the adverse event risk before initiating bevacizumab therapy, patient counseling should be documented, and these patients may benefit from routine prophylaxis with aspirin.

Studies of vatalanib (PTK787), a selective inhibitor of VEGF receptor tyrosine kinases, added to FOLFOX therapy showed that the addition of the inhibitor did not further improve outcomes for chemotherapy-naïve or second-line patients. On the contrary, in the first-line phase III trial presented at the American Society of Clinical Oncology 2005 annual meeting, vatalanib treatment was associated with a nearly 2-fold increase in discontinuations due to adverse events.30

DUAL INHIBITOR THERAPY

Encouraging results on dual antibody therapy (anti-VEGF and anti-EGF receptor) in advanced colorectal cancer were recently presented. In patients who were refractory to irinotecan (most of whom had also received prior oxaliplatin), the addition of bevacizumab to cetuximab or to cetuximab and irinotecan increased response rates and prolonged time to progression compared to historic controls.31

Summary

Salvage therapy with the EGF inhibitor cetuximab has produced clinically relevant treatment responses. In combination with front-line chemotherapies, cetuximab therapy has shown impressive response rates in phase II trials that warrant confirmation in ongoing phase III studies. In combination with first- and second-line chemotherapy, the VEGF inhibitor bevacizumab has been shown to increase response rates, progression-free survival, and overall survival in patients with advanced colorectal cancer. Even in patients at higher risk for serious side effects, such as arterial events, bevacizumab therapy is associated with improved outcomes. Dual antibody therapy with bevacizumab and cetuximab

Figure 4. Phase III Trial of Bevacizumab in MCRC: Survival

HR = hazard ratio; IFL = irinotecan combined with 5-fluorouracil/leucovorin; MCRC = metastatic colorectal cancer.
with or without conventional chemotherapy appears to be a very active combination, increasing time to tumor progression and response rates compared to historic controls. Treatment strategies that add biologic agents to cytotoxic agents appear to improve the efficacy of chemotherapies and are fast becoming standard of care.

**TOXICITY**

The TREE trials studied the best way to deliver oxaliplatin in combination with a fluoropyrimidine, randomizing patients to modified FOLFOX-6, CapOx, and bolus 5-FU/LV plus oxaliplatin (bFOL). Once bevacizumab was approved by the US Food and Drug Administration, it was added to all 3 arms to form the TREE-2 trial. The TREE trials showed that FOLFOX and CapOx were both more efficacious than bFOL. When bevacizumab was added to these regimens, higher response rates were observed, but no increase in time to treatment failure was observed in comparison between the sequential TREE-1 and TREE-2 trials. This result is conceivably explained by the cumulative neurotoxicity of oxaliplatin-based therapies. Typically, patients can tolerate these regimens for approximately 6 months up to a cumulative oxaliplatin dose of approximately 850 to 1000 mg/m². Because time to treatment failure is a composite endpoint reflecting disease progression and toxicity, no increased time to treatment failure is achieved when bevacizumab is added to oxaliplatin-containing regimens. An analysis of the FOLFOX-4 arm in Intergroup trial N9741 demonstrated, even in the prebevacizumab era, significant differences between median time to treatment failure (5.8 months) and median time to tumor progression (9.3 months) on FOLFOX. This means that even after discontinuation of oxaliplatin, benefits of therapy are maintained for some time (Figure 5). The results of a trial of intermittent administration of FOLFOX (OPTIMOX) showed that removing oxaliplatin for 6 months while continuing 5-FU/LV before reintroducing it did not impair treatment efficacy, but it did reduce neurotoxicity.

**PROPOSED TREATMENT ALGORITHM**

The current studies suggest that exposing patients to as many of the standard of care agents as possible in a strategic approach will provide maximum benefit. Figure 6 depicts an example of such a treatment algorithm, in which potentially curable patients receive intensified initial chemotherapy using a combination of FOLFOX and dual antibody therapy (bevacizumab/cetuximab) to maximize tumor shrinkage and enhance chances for secondary resection of metastases. The primary goal of therapy for patients who do not appear to be candidates for a curative approach is pal-
liative, meaning extending the duration of survival and maintaining quality of life on therapy. For those patients, induction therapy with bevacizumab and FOLFOX or FOLFIRI to control tumor growth followed by sequential use of all 5 active drug classes (fluoropyrimidines, irinotecan, oxaliplatin, bevacizumab, and anti-EGF receptor antibody) with minimized toxicity is a rationale strategy.

CONCLUSIONS

At present, FOLFOX or FOLFIRI appear to be the best first-line chemotherapy backbone. For most patients, sequential administration of chemotherapies will provide the most benefit, with biologic agents clearly adding to the efficacy of cytotoxic treatments. In this context, bevacizumab has been shown to prolong overall survival when added to chemotherapy, and cetuximab increases response rates in multimodality approaches. Dual antibody therapy with bevacizumab and cetuximab appears to be potent treatment in combination with chemotherapy and has been shown to improve outcomes according to several measures. Phase III studies exploring the benefits of dual biologic therapy added to modern conventional chemotherapy regimens are ongoing and will conceivably define the future standard of care in the management of advanced colorectal cancer.

DISCUSSION

Dr Fong: I want to make sure that we distinguish between neoadjuvant and palliative approaches. Neoadjuvant therapy is given to someone who is resectable from the start, someone who receives chemotherapy as induction. Palliative therapy is given to someone who is not resectable with the hope that they respond and become a surgical candidate. The 2 populations are very different and need to be viewed differently.

Dr Grothey: I agree. These are 2 different patient populations. We can cure patients with resectable tumors right now. Thirty percent of resectable patients survive disease-free for 5 years, but we might do better by treating with chemotherapy first. So, how would you define this now? Neoadjuvant for resectable disease, and the other is?

Dr Choti: How about calling it downsizing therapy? I think the paradigm we are defining is curative intent mode versus palliative intent mode. I would call chemotherapy administered preoperatively in an initially unresectable patient but with the goal to convert to resectable as induction chemotherapy. This is in distinction to a case when curative intent is not a realistic option, even if a significant response occurs. I would reserve the term “palliative chemotherapy” for these cases.

Dr Fong: I agree that delineating between these 2 is going to be important in how we plan strategies for these subsets of the treatment paradigm. Occasionally, someone will move from the palliative group to the resectable group, and I think we need to take this into consideration.

Dr Grothey: I think it is important to let our mindset play a role. That is why I do not like the term “palliative.” It implies a situation in which there is no curability, and our primary goal is to keep the patient alive as long as possible. We need to make a decision early on and decide when very aggressive neoadjuvant treatment is worthwhile because we cannot treat all patients with dual antibody therapy up front. For instance, if a patient’s long-term chance for overall survival is only 5%, should we use more aggressive treatment with more adverse side effects?

Dr Choti: Let’s focus some of the discussion on the options for regimens of systemic therapy.

Dr Althaus: It seems to me that most patients on adjuvant therapy are receiving FOLFOX. When those patients present with metastatic disease, does that change your approach?

Dr Grothey: A lot of patients who present with metastatic disease had not received adjuvant therapy. Only 20% to 30% of patients in some of the large trials had prior adjuvant therapy. I agree that over time we will see more patients with adjuvant therapy, and many of those will have received FOLFOX. I think the decision to reintroduce FOLFOX depends on how much time has passed since the end of adjuvant chemotherapy, the biologic characteristics of the patient and tumor, patient risk level, and, of course, initial response to FOLFOX. I am more willing to switch over to FOLFIRI if the patient did not respond to FOLFOX initially.

Dr Althaus: Does the decision to switch therapies depend on how long it has been since the patient was last treated?

Dr Grothey: Yes. Suppose you had a patient who was treated with FOLFOX after 6 of 12 positive lymph nodes were resected. If this patient recurred 4 years later,
I would say FOLFOX was an effective adjuvant treatment because of the initial poor prognosis of this patient, and I would reuse FOLFOX, knowing by that time neurotoxicity should have regressed. If the same patient had recurred within 8 or 12 months, I would say it would not be wise to reuse FOLFOX. We will develop a feel for how to use these agents most effectively, and future trials will provide practical guidance.

Dr Choti: However, we do not have clear evidence about efficacy, and cases are not always clear enough to allow choice of first-line therapy based on whether the adjuvant therapy was effective. We will probably never know whether an individual adjuvant therapy was effective.

Dr Grothey: I think we will never have level 1 evidence for all clinical settings, thus over time we will develop treatment paradigms that tell us when to reuse therapies and when to use alternatives.

REFERENCES


