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Current Status of Targeted Therapies in the Treatment of Metastatic Colorectal Cancer

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The incidence of colorectal cancer (CRC) has continuously increased and CRC is a major cause of cancer-related death. Systemic chemotherapy has resulted in a significant improvement in overall survival in metastatic CRC. The development of biologic agents for the treatment of CRC has additionally expanded the options for the treatment. Cetuximab is useful in KRAS wild type tumors in combination with chemotherapy for metastatic disease in both the first and second line settings. It is also used as monotherapy after failure of both irinotecan and oxaliplatin containing regimens. Panitumumab has similar indications, and is primarily used in patients intolerant to cetuximab due to hypersensitivity reactions. Bevacizumab is primarily used as first line and second line therapy in metastatic CRC. However, the optimal way and duration to combine these chemotherapeutic agents are not yet established.

Key Words: Colorectal cancer, Bevacizumab, Cetuximab, Panitumomab

IINTRODUCTION

The incidence of colorectal cancer (CRC) has continuously increased and CRC is the second cause of cancer-related death in the United States.[1] Approximately 75% of these patients are diagnosed with early stage disease (stages I-III) who are potentially cured with surgery alone or with the addition of adjuvant chemotherapy.[2] Adjuvant chemotherapy has resulted in a significant improvement in overall survival (OS).[2] The 5-year OS for patients with Stage III colon cancer is 60%, however this decreases to 5% in patients with metastatic disease, emphasizing the importance of adjuvant chemotherapy to eliminate micrometastatic disease present at the time of curative surgical excision.[3]

Multiple randomized controlled trials have established the benefit of 5-fluorouracil (5-FU) based regimens in the adjuvant treatment for CRC.[4,5] Adding oxaliplatin to 5-FU/leucovorin (LV) improves disease free survival (DFS) for Stage II/III colon cancer with decreases in relative recurrence risk by 20-23%.[6,7] Irinotecan has proven benefit in metastatic CRC.[8]

The development of biologic agents in mid-2000s, namely bevacizumab and cetuximab, and their integration with conventional cytotoxic agent for the treatment of CRC has additionally expanded the options for the treatment. Their dramatic success has led to further clinical studies of targeted therapy in colorectal cancer, making it one of the most promising areas of cancer research.[9]

This review will discuss the current status of targeted therapies for metastatic CRC.

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITOR

The epidermal growth factor receptor (EGFR) regulates signaling pathways involved in cell differentiation, cell proliferation and angiogenesis. Cetuximab (Erbitux®) is a recombinant chimeric human murine immunoglobulin antibody that binds to and inhibits EGFR. A similar drug, panitumumab (Vectibix®), is a fully human monoclonal antibody that inhibits EGFR. By inhibiting EGFR, cetuximab and panitu- mumab act via multiple mechanisms including G1 cell cycle arrest, induction of apoptosis, inhibition of tumor angiogenesis and activated antibody dependent cellular toxicity.[3,10] Importantly, the anti-EGFR agents have shown clinical success only in tumors that are KRAS wild type, and not in those with KRAS activating mutations, as these mutations cause consti-

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tutive activation of signaling cascades downstream to EGFR.[11] Therefore, KRAS mutation status is routinely tested prior to initiation of anti-EGFR therapy. Similarly, the anti-EGFR agents are most effective in tumors that are BRAF wild type.[11,12]

Cetuximab monotherapy was compared to best supportive care (BSC) in a randomized trial of 572 patients who had failed or were intolerant of all recommended therapies.[13] Median overall survival was significantly better with cetuximab (6.1 vs 4.6 months). In a subsequent analysis, the benefits of cetuximab were restricted to patients whose tumors lacked a KRAS mutation.[14]

The CRYSTAL (cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer) trial was a randomized, open-label, multi-center study compraring 14-day cycles of cetuximab plus irinotecan, fluorouracil, and leucovorin (FOLFIRI) and FOLFIRI alone as first-line treatment for metastatic colorectal cancer.[15] The hazard ratio (HR) for progression-free survival (PFS) in the cetuximab-FOLFIRI group as compared with the FOLFIRI group was 0.85 (95% confidence interval (CI), 0.72 to 0.99; p=0.048). There was no significant difference in the OS between the two treatment groups (hazard ratio, 0.93; 95% CI, 0.81 to 1.07; p=0.31). The benefit of cetuximab was limited to patients with KRAS wild-type tumors.

In contrast to irinotecan-based regimens, the benefit of adding cetuximab to a first-line oxaliplatin-based regimen remains uncertain.[16,17]

The benefit of panitumumab monotherapy was initially shown in a multicenter trial in which 463 patients refractory to 5-FU, irinotecan, and oxaliplatin were randomly assigned to best supportive care (BSC) with or without panitumumab.[18] The objective response rate with panitumumab was 10 percent, and 27 percent had stable disease. The corresponding rates with BSC alone were 0 and 10 percent. Patients receiving panitumumab were significantly more likely to be alive and progression-free at 8 weeks (49 vs 30 percent).

The Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) was designed to evaluate the efficacy and safety of panitumumab plus infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as initial treatment for mCRC.[19] In patients with wild-type (WT) KRAS tumors, panitumumab-FOLFOX4 significantly improved PFS compared with FOLFOX4 (median PFS, 9.6 vs 8.0 months, respectively; HR, 0.80; 95% CI, 0.66 to 0.97; p=0.02). This study also underscores the importance of KRAS testing for patients with mCRC.

Cetuximab is useful in KRAS wild type tumors in combination with chemotherapy for metastatic disease in both the first and second line settings. It is also used as monotherapy after failure of both irinotecan and oxaliplatin containing regimens. Panitumumab has similar indications, and is primarily used in patients intolerant to cetuximab due to hypersensitivity reactions.[3]

VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITOR

Vascular endothelial growth factor (VEGF) regulates angiogenesis both in health and disease, and contributes to angiogenesis in malignancy.[20] For this reason, bevacizumab (Avastin®), a humanized monoclonal antibody to circulating vascular endothelial growth factor A (VEGF-A) was developed. Preclinical studies have shown multiple mechanisms of action for bevacizumab including inhibition of angiogenesis[21] by pruning of existing vessels and normalization of aberrant vessels which is thought to improve delivery of concurrently administered chemotherapy.[22] However, bevacizumab is thought to be cytostatic rather than cytotoxic, which may explain its success only in combination with cytotoxic chemotherapy, rather than as monotherapy.[21]

In a pooled analysis of trials comparing chemotherapy with and without bevacizumab in the first-line setting, the addition of bevacizumab was associated with a significant 19% reduction in the risk of death (HR 0.81, 95% CI 0.70-0.93), but this translated into a median OS advantage of only 2 months (19.8 versus 17.6 months).[23] PFS was also significantly improved (HR 0.58, 95% CI 0.46-0.73) but the advantage was also limited to approximately 2 months (median PFS 9.1 vs 6.9 months). These modest advances come at a cost of treatment-related side effects, including bleeding, hypertension, bowel perforation, and thromboembolic events. However, although there are these potentially serious outcomes, they are not common.

The benefit of adding bevacizumab to irinotecan was initially shown in a trial of 813 patients with metastatic CRC who were randomly assigned to irinotecan, bolus fluorouracil, and leucovorin (IFL) with or without bevacizumab.[24] The median duration of survival was 20.3 months in the group given IFL plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a HR for death of 0.66 (p<0.001). The median duration of PFS was 10.6 months in the group given IFL plus bevacizumab, as compared with 6.2 months in the group given IFL plus placebo (HR, 0.54; p<0.001).

Bevacizumab also adds benefit to first-line FU/LV and capecitabine. In two randomized phase II trials in which previously untreated patients were assigned to bolus FU/LV with or with-

out bevacizumab, response rates were approximately twofold higher with bevacizumab, and median survival was extended by 7.7 and 3.7 months for the two doses, respective.[25,26]

The benefit of adding bevacizumab to a first-line oxaliplatin-based regimen is less clear and the results from randomized trials are conflicting.[27-29]

Bevacizumab improves PFS and OS in the treatment of metastatic CRC. However, there are no reliable predictors such as KRAS status for EGFR inhibitors. The antitumor activity of VEGF inhibition is independent of KRAS status, or VEGF receptor expression.[30]

Bevacizumab is primarily used as first line and second line therapy in metastatic CRC based on studies showing improved OS.[3,24,28] Bevacizumab is also used for continuation therapy at progression of metastatic disease based on data showing improved OS with ongoing bevacizumab use after progression when the chemotherapy backbone was changed.[31]

CONCLUSIONS

The most patients with metastatic CRC cannot be cured, although either isolated liver or lung metastasis are potentially curable with surgery. Systemic chemotherapeutic agents (5-FU, irinotecan, oxaliplatin) showed significant improvements in PFS and OS. The approval of three humanized monoclonal antibodies that target EGFR (cetuximab and panitumomab) and VEGF (bevacizumab) has changed the treatment pattern for metastatic CRC. These agents targeting specific molecules produce meaningful improvements in efficacy for the treatment of metastatic CRC. However, the optimal way and duration to combine these chemotherapeutic agents are not yet established.

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