AHFS Final Determination of Medical Acceptance: Off-label Use of Capecitabine in Combination with Oxaliplatin for the Adjuvant Treatment of Stage III Colon Cancer

Drug/Drug Combination: Oxaliplatin and capecitabine

Off-label Use: Adjuvant treatment of stage III colon cancer

Criteria Used in Selection of Off-label Use for Review:

- Clinical results from a randomized phase 3 trial

Strength of Evidence: Level 2 (Moderate strength/quality)

Strength of Study End Point(s): Disease-free survival

Grade of Recommendation: Reasonable choice (Accepted, treatment option)

Narrative Summary:

Use:

Capecitabine has been used in combination with oxaliplatin† (CapeOx) as adjuvant therapy in patients with stage III colon cancer who have undergone complete resection of the primary tumor.[10001, 10002, 10003, 10006]

Adjuvant therapy with oxaliplatin in combination with IV fluorouracil and leucovorin has been shown to increase disease-free and overall survival in patients with stage III colon cancer who have undergone complete resection of the primary tumor.[10004, 10005] Therefore, efficacy and safety of oxaliplatin in combination with capecitabine (a prodrug of fluorouracil) as adjuvant therapy in patients with stage III colon cancer have been evaluated in an open-label, randomized phase 3 study (NO16968; XELOXA).[10001]

In this study, 1886 patients were randomized to receive either combination therapy with oxaliplatin (130 mg/m^2 administered by IV infusion over 2 hours on day 1) and capecitabine (1 g/m^2 administered orally twice daily on days 1–14) on a 3-week cycle for 8 cycles or combination therapy with IV fluorouracil and leucovorin (Mayo Clinic or Roswell Park regimen).[10001] The Mayo Clinic regimen consisted of fluorouracil 425 mg/m^2 administered by rapid IV injection (”bolus”) and leucovorin 20 mg/m^2 administered by rapid IV infusion on days 1–5 of each 4-week cycle for a total of 6 cycles (24 weeks), and the Roswell Park regimen consisted of fluorouracil 500 mg/m^2 administered by rapid IV injection (”bolus”) and leucovorin 500 mg/m^2 administered as a 2-hour IV infusion on day 1 of weeks 1–6 of each 8-week cycle for a total of 4 cycles (32 weeks).[10003] Patients were enrolled no more than 8 weeks following surgery with curative intent, by which time full recovery from surgery was required.[10001] The median age of patients was 61–62 years.[10001] Most patients (99%) enrolled in the study had a baseline ECOG performance status of 0 or 1.[10001] The primary measure of efficacy was disease-free survival.[10001]

At a median follow-up of 74 months, patients who received capecitabine in combination with oxaliplatin had higher disease-free (66.1 versus 59.8%; hazard ratio: 0.8) and relapse-free (69.3 versus 62.2%; hazard ratio: 0.78) survival rates compared with patients who received fluorouracil and leucovorin.[10002] At a median follow-up of 83 months, patients who received capecitabine in combination with oxaliplatin also had a higher overall survival rate (74.4 versus 69.6%; hazard ratio: 0.83) compared with those who received fluorouracil and leucovorin.[10002] Subgroup analysis based on prognostic factors (e.g., age, regional lymph node involvement, baseline carcinoembryonic antigen [CEA] concentration) suggested that the effect of capecitabine in combination with oxaliplatin on disease-free and overall survival was consistent across the subgroups, including those 70 years of age or older; however, the effect size appeared to be reduced in patients 70 years of age or older compared with younger patients.[10002] Neurosensory toxicity (any grade: 78 versus 8%; grade 3 or 4: 11 versus less than 1%), grade 3 or 4 hand-foot syndrome (5 versus less than 1%), and grade 3 or 4 thrombocytopenia (5 versus less than 1%) occurred more frequently in patients receiving capecitabine in combination with oxaliplatin, while grade 3 or 4 neutropenia (9 versus 16%), febrile neutropenia (less than 1 versus 4%), and stomatitis (less than 1 versus 9%) occurred more frequently in those receiving fluorouracil and leucovorin.[10001, 10003]

Use of combination therapy with oxaliplatin and capecitabine also was investigated in a randomized, multicenter, phase 3 study in patients with high-risk stage II or stage III colorectal cancer who had undergone complete resection of the primary tumor; however, interpretation of the results is limited by the failure to meet the planned accrual of 800 patients in the study to demonstrate superiority.[10006] In this study, 408 patients were randomized to receive either combination therapy with oxaliplatin (130 mg/m^2 on day 1) and capecitabine (1 g/m^2 twice daily on days 1–14) on a 3-week cycle for 8 cycles or combination therapy with an oxaliplatin, fluorouracil, and leucovorin (modified FOLFOX6) regimen on a 2-week cycle for 12 cycles.[10006] At a median follow-up of 74.7 months, median disease-free and overall survival had not been reached; however, 3-year disease-free and overall survival rates were similar between patients receiving capecitabine in combination with oxaliplatin (79.5 and 86.9%, respectively) compared with patients receiving modified FOLFOX6 (79.8 and 87.2%, respectively).[10006]

Based on current evidence, combination therapy with oxaliplatin and capecitabine is a reasonable choice (accepted, treatment option) for use as adjuvant therapy in patients with stage III colon cancer who have undergone complete resection of the primary tumor.

Dosage:

When capecitabine has been used in combination with oxaliplatin (CapeOx) as adjuvant therapy following the complete resection of the primary tumor in patients with stage III colon cancer, capecitabine 1 g/m^2 has been administered orally twice daily on days 1–14 and oxaliplatin 130 mg/m^2 has been administered by IV infusion over 2 hours on day 1 of each 3-week cycle.[10001,10006] Treatment has been continued for 8 cycles of therapy.[10001,10006]

References:

10001. Haller DG, Tabernero J, Maroun J et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol*. 2011; 29:1465-71.

10002. Schmoll HJ, Tabernero J, Maroun J et al. Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial. *J Clin Oncol*. 2015; 33:3733-40.

10003. Schmoll HJ, Cartwright T, Tabernero J et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. *J Clin Oncol*. 2007; 25:102-9.

10004. Yothers G, O'Connell MJ, Allegra CJ et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol*. 2011; 29:3768-74.

10005. André T, de Gramont A, Vernerey D et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. *J Clin Oncol*. 2015; 33:4176-87.

10006. Pectasides D, Karavasilis V, Papaxoinis G et al. Randomized phase III clinical trial comparing the combination of capecitabine and oxaliplatin (CAPOX) with the combination of 5-fluorouracil, leucovorin and oxaliplatin (modified FOLFOX6) as adjuvant therapy in patients with operated high-risk stage II or stage III colorectal cancer. *BMC Cancer*. 2015; 15:384-5.

Oncology Expert Committee Voting Results:

Proposed Level of Evidence:

Level 2 (Moderate strength/quality); disease-free survival

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 2 votes

Reasonable choice (Accepted, treatment option): 3 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:

Based on current evidence, combination therapy with oxaliplatin and capecitabine is a reasonable choice (accepted, treatment option) for use as adjuvant therapy in patients with stage III colon cancer who have undergone complete resection of the primary tumor.

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Oncology Expert Committee Members' Comments:

Comments on Draft Narrative Summary:

Reviewer #1: Well-designed, large study with appropriate long-term follow-up and endpoints. Toxicity is expected/reasonable for all patients and all subgroups seemed to benefit. Would consider CapeOx and FOLFOX both as reasonable options in stage III adjuvant setting.

Not necessary to include as reference due to limitations, but Pectasides et al [in] *BMC Cancer* 2015; 15:384-5 compared FOLFOX and CapeOX and showed similar outcomes, further supporting either regimen's use in stage III adjuvant setting.

Reviewer #3: Good summary.

References appropriate.

Reviewer #5: Need to be consistent listing grade ≥3 AEs. Also need to mention that for 5FU/LV patients on Mayo and Roswell [regimens] were combined for these toxicity numbers and that there were some differences in the two [5]FU/LV arms.

Comments on Evidence Table:

Reviewer #5: Should list the grade 3/4 [toxicity] to be consistent (under "neurosensory toxicity"); also need to clarify that the [5]FU/LV numbers reflect Mayo and Roswell; should list grade ≥3 as above (under "febrile neutropenia" and "stomatitis"); under "response", state months under "7-year DFS" and "RFS" for consistency.

Comments on Proposed Consensus Recommendation:

None.

Participants:

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AHFS Oncology Expert Committee Members (reviewing and voting): Sandra Kurtin, RN, MS, AOCN, ANP-C; Mandy Gatesman, Pharm.D., BCOP; Robert Mancini, Pharm.D., BCOP; LeAnn Norris, Pharm.D., BCPS, BCOP; Ron Walters, M.D., MBA, MHA, MS

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

Publication Date: November 9, 2016