SESSION 3: ADVANCED COLON CANCER

Is There an Optimal Treatment Sequence in the Palliative Management of mCRC? What Have we Learned From FIRE-3 and 80405?

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Over the course of the last fifteen years, there has been significant progress in the development of therapies for the treatment of metastatic colorectal cancer. The development of these treatments has resulted in an impressive improvement in the overall survival of patients with this disease. Requisite to the development of these new agents has been a need to establish the proper sequence and combinations of these therapies, to minimize toxicity while maximizing benefit. The current established paradigm suggests that, in both first and in second lines of therapy in metastatic disease, patients should be treated with a combination of a chemotherapy doublet and a monoclonal antibody. The chemotherapy doublet consists of a fluoropyrimidine paired with either oxaliplatin or irinotecan. For the antibody, two class options exist: either an anti-VEGF (bevacizumab in first line treatment) or an anti-EGFR (either cetuximab or panitumumab). With this dual option, the natural question that has arisen is whether one antibody class is superior to the other, and thus should be preferred in first line therapy.

Several trials have been conducted in an endeavor to determine if one antibody is preferable in the first line setting. The FIRE-3 study, published in 2014, randomized 592 patients with metastatic colorectal cancer to chemotherapy with FOLFIRI and cetuximab or FOLFIRI and bevacizumab; patients were treatment naïve in the metastatic setting. As the understanding of KRAS mutational status evolved while the trial was ongoing, the intention-to-treat population was modified, so that all patients had tumors that were KRAS wildtype at exon 2. There were no statistically significant differences in the primary endpoint of objective response, nor in secondary endpoints of ORR or PFS, and safety profiles were similar. However, overall survival demonstrated a statistically significant improvement, noting that this improvement did not manifest until patients had been on study for 18-24 months. A retrospective evaluation of patients whose tumors were extended-RAS wildtype demonstrated an OS benefit as well, and no benefit in other endpoints. While the investigators suggest, as an interpretation of these results, that FOLFIRI/cetuximab should be first line therapy for patients with RAS-wildtype metastatic colorectal cancer over FOLFIRI/bevacizumab, this should be accepted with caution, noting the lack of corresponding PFS preference, small event numbers, and wide confidence intervals. A similar study, the PEAK study, evaluated 285 patients with metastatic, KRAS-wildtype colorectal cancer, also in the first line setting. In PEAK, patients received FOLFOX chemotherapy, and were randomized to an antibody pairing of either panitumumab or

bevacizumab. Survival benefits were variable with different endpoints and cohorts, and no clear benefit was established with either treatment approach. The largest study to compare antibody selection, the CALGB/SWOG 80405, evaluated 1137 patients. Patients were treatment naïve in the first line metastatic setting; the trial was amended so that all patients in the final intention-to-treat analysis had tumors that were KRAS wildtype. Patients were treated with either FOLFOX or FOLFIRI chemotherapy, assigned at the treating physician's discretion, with FOLFOX being favored at 3:1. Patients were then randomized to therapy with either cetuximab or panitumumab. A number of cohorts were evaluated. These included all chemotherapy with bevacizumab versus cetuximab, FOLFOX with each antibody, and FOLFIRI with each antibody. In each cohort, there was no significant difference in any endpoint.

The sum total of these studies suggest than any combination could be correct but that no clear preference is established. Importantly, no approach seems to be inferior. Thus these data can be used in combination with other factors to select best therapy for the individual patients. Such factors could include lines of therapy, costs, and toxicity. For example, deferring anti-EGFR antibody to a later line would allow the creation of a third line of treatment, thus extending available treatment options for the individual. The higher cost of cetuximab, in combination with its more frequent dose schedule compared to bevacizumab, is substantial; if only one antibody is ever to be used to treat a patient, this could show preference for bevacizumab. Quality of life was assessed in 80405 and there was no global difference between the different arms of therapy. There were greater reports of skin toxicity with cetuximab, which is expected, but this did not impact global quality of life reports, possibly because the patients understood that this toxicity corresponded to treatment effect.

Available evidence suggests that all first line therapy for metastatic colorectal cancer should include a monoclonal antibody unless contraindicated by specific patient characteristics. There is no clear benefit, but also no harm, to the selection of anti-VEGF or anti-EGFR as this antibody in the first line, noting that mutant RAS status should exclude use of an anti-EGFR. Suggestion of overall survival benefit in the FIRE-3 study is hypothesis generating, but in the context of a late separation of benefit (18-24 months), equivalent PFS, and contradictory data in other studies, further scrutiny is necessary. These data, taken into context along with other patient factors, can help to individual antibody selection to the patient.

References:

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