CLINICAL VIGNETTE

What's New in Adjuvant Colon Carcinoma Management: A Case Report

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Case Report

A 50-year-old woman presented to her primary care doctor with progressive fatigue, exercise intolerance, and palpitations. Initial testing identified iron-deficiency anemia with a hemoglobin of 8.0 g/dL. Diagnostic colonoscopy demonstrated a sigmoid colon adenocarcinoma. Staging CT scans did not identify any metastatic disease and the patient underwent robotic sigmoid colectomy. Surgical pathology revealed an invasive adenocarcinoma that invaded into the muscularis propria and involved 3 of 19 lymph nodes, consistent with stage III colon cancer. Surgical margins were negative.

The patient was referred to medical oncology for consideration of adjuvant chemotherapy. She was otherwise in good health and did not take any prescription medications. She did not have a family history of colorectal carcinoma. She regularly consumed red meat and drank soda.

Medical oncology recommended adjuvant chemotherapy with 3 months of capecitabine and oxaliplatin. At the completion of chemotherapy, she was encouraged to make numerous life-style modifications to reduce her chance of colorectal cancer recurrence including increased fruit and vegetable intake, 2 servings of tree nuts a week, and decreased intake of red and processed meats.

Discussion

For nearly the last 2 decades, the standard of care adjuvant therapy for resected stage III colon cancer has been 6 months of combination chemotherapy with a fluoropyrimidine agent and oxaliplatin. The pivotal MOSIAC and NSABP C-07 trials demonstrated that this approach improved cure rates in stage III colon cancer by about 10%.[1,2] However, this survival benefit came at cost – toxicity from chemotherapy, most notably oxaliplatin-induced peripheral neuropathy. A significant number of patients treated with 6 months of oxaliplatin develop neuropathy and many have significant symptoms that last for years after their last oxaliplatin infusion.

In an attempt to minimize the toxicity while maintaining the efficacy of adjuvant chemotherapy, the IDEA trial was initiated (International Duration Evaluation of Adjuvant Therapy). The IDEA trial was a non-inferiority trial that sought to determine if 3 months of therapy was not worse than 6 months in terms of 3 year disease-free survival (DFS), a known surrogate for overall survival in adjuvant colon cancer studies. The study randomized nearly 13,000 patients with stage III colon cancer in 12 countries to either 3 or 6 months of chemotherapy with a fluoropyrimidine(5-fluorouracil or capecitabine) and oxaliplatin. Despite failing to demonstrate statistical non-inferiority of 3 months of therapy, the results of the study were practice changing.

When analyzing all patients on an intention-to treat basis, the 3 year DFS rates were 74.6% vs 75.7% for 3 and 6 months of therapy respectively. The 0.9 percentage point difference was insufficient to demonstrate statistical non-inferiority. When discussing the study results with a patient, it is important to remember, that the non-inferiority margin in any study is arbitrary. A pre-planned subset analysis of patients with low-risk stage III colon cancer, demonstrated that 3 months was non-inferior to 6 months. In the high-risk group, non-inferiority could not be demonstrated – however the difference in year DFS was small, 62.7% vs 64.4%.[3]

Importantly, there were significant differences in toxicity, favoring the 3 month arm. About 15% of patients in the 3-month arm developed persistently symptomatic neuropathy, versus 45% of patients in the 6-month arm. Additionally, rates of other toxicities such as diarrhea, myelosuppression, and hand-foot syndrome were higher with 6 months of chemotherapy. The data from from the IDEA study were clear – 3 months of chemotherapy resulted in significantly less toxicity but only a marginal decrease in efficacy.

This data changes the management of patients with resected stage III colon cancer. For patients with low-risk disease, the recommendation is 3 months of a fluroropyrimidine and oxaliplatin. While for patients with high-risk disease, there should be a discussion to determine for an individual patient whether the slight improvement in outcome is worth the substantially higher risk of toxicity. Given the results of the IDEA study, the patient in the vignette was given 3 months of chemotherapy for low-risk stage III colon cancer. If the patient were diagnosed a few years ago, the recommendation would have been for 6 months of adjuvant chemotherapy.

The CALGB 89803 trial was a study of 2 different adjuvant chemotherapy regimens in patients who had undergone surgery for stage III colon cancer. The study prospectively gathered, extensive data about physical activity, diet, supplement intake, and smoking. To determine the association of dietary patterns

on cancer recurrence and mortality risk in established cancer, dietary patterns were divided into 2 groups: Western and prudent. The Western dietary pattern was characterized by higher intake of red and processed meats, sweets and desserts, French fries, refined grains, and sugar-sweetened beverages. In contrast, the prudent diet was characterized by higher intake of fruits, vegetables, legumes, fish, poultry, and whole grains. With a median of 5.3 years of follow up, strong associations emerged. The Western diet was significantly associated with an increased risk of colon cancer recurrence and mortality as well as all-cause mortality. The patients with "most Western diet" – highest intake of that dietary pattern - were 3 times more likely to experience disease recurrence. The increased risk of colon cancer recurrence and mortality did not change when controlling for other factors known to predict for colon cancer recurrence, such as, number of positive lymph nodes or post-operative carcinoembryonic antigen level. Interestingly, the prudent dietary pattern did not seem to have an association on the rate of colon cancer recurrence or colon cancer mortality.[4]

A subsequent prospective cohort study using the same data collected from the CALGB 8903 trial sought to determine if an association existed for nut intake with colon cancer recurrence and mortality. The data suggested that increased nut consumption was associated with a significant decrease in risk of colon cancer recurrence and morality. Subset analysis suggested the strongest association with greater than 2 servings of nuts a week and the benefit was confined to tree nuts. Similarly, to the data from the dietary patterns study, the risk reduction associated with nut intake remained when controlling for biologic features that predict for colon cancer recurrence, including number of positive lymph nodes or adverse genetic mutations. The association also persisted when controlling for other potentially confounding factors including Western versus prudent diet.[5]

Given the findings of these 2 analyses, in addition to the 3-month course of chemotherapy, the patient was recommended to follow a more "prudent diet" and to incorporate tree nuts into her regular diet.

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