Managing Choices for Older Patients with Colon Cancer: Adjuvant Therapy

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OVERVIEW

Colon cancer is among the most common cancers in the United States, and the median age of patients at diagnosis is 70. Medical oncologists are commonly asked to comprehensively evaluate elderly patients to estimate individual risk/benefit ratios for adjuvant treatment. Although 40% of patients with colon cancer are elderly, clinical trials enroll mainly younger patients. Consequently, we are forced to depend on subgroup analyses, observational studies, and personal experience to guide recommendations. Decision-making in adjuvant therapy for colon cancer is increasingly complex, as we subdivide patients with stage II to III colon cancer by molecular as well as anatomic staging to predict which are likely to benefit from chemotherapy and then whether the addition of oxaliplatin to 5-fluorouracil (5-FU) is worth the toxicity. It is likely that the tumor biology of younger and older patients differs, and more research is needed to dissect out the biologic heterogeneity of both the tumors and their elderly hosts to help guide treatment. We recognize that our evaluations should not solely be based on temporal age and factor physiology, pharmacology, psychology, functional status, and social support into these considerations. Older patients who are treated must be monitored closely for toxicities when undergoing treatment. Although there is a clear need for clinical trials in this population, treatment decisions confront us today in the absence of definitive evidence. How can we help our patients navigate through these important choices?

Colon cancer is the third most common cancer in the United States and the second leading cause of cancer death. It is a cancer that disproportionally afflicts older people. Forty percent of colon cancer cases are diagnosed over the age of 75 years, and increasing longevity means this is an increasingly common clinical issue.[1] Life expectancy at age 70 is an additional 17.8 years for women and 14.1 years for men, and 80 year-old women are expected to live 10.3 more years and men 8.1 more years.[2] The median age at diagnosis of colon cancer is 70 years, yet there is a paucity of trials including the elderly population.[3] This may be because of trial eligibility criteria, in which patients above a certain age are explicitly excluded or because older patients fail to meet eligibility because of suboptimal organ function or blood counts. In addition, oncologists may be reluctant to enroll elderly patients, and the older population may be less motivated to enroll on clinical trials because of their increased testing and time requirements. Thus, adjuvant chemotherapy trials for colon cancer enroll mainly younger patients, and data relevant to older populations are based primarily on subgroup analyses, meta-analyses, or population-based analyses. Population-based studies of patients managed in community practices show that elderly patients receive less chemotherapy than younger patients. A retrospective chart review of 10 oncology practices in the United States reported that 58% of patients who were older than 65 years received chemotherapy, in comparison with 84% patients who were 65 years or younger ($p < 0.001$).[4]

ASSESSING THE ELDERLY PATIENT

What defines an elderly patient, and do we adequately assess them in clinical practice? It is a disservice to classify patients based on their temporal age alone, because there are several other factors to be taken into account, including physiologic factors, pharmacologic factors, functional status, and social situation. Older patients often have a different physiology from their younger counterparts, and this in turns affects their tolerance of chemotherapy. Their body composition (increased fat content), gastrointestinal tract (decreased motility and digestive enzymes), chronic organ insufficiency (heart, renal, and liver function), decreased drug clearance, and reduced hematologic reserve can all affect chemotherapy tolerance. In addition, elderly patients are often taking multiple medications, which may interact with chemotherapy. For example, capecitabine is excreted by the kidneys and known to interact with coumadin. Thus, a patient with compromised renal function taking coumadin in addition to capecitabine should be closely monitored for toxic effects and requires intensive international normalized ratio (INR)

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monitoring. Comorbid medical conditions may also preclude using some therapies. For example, oxaliplatin chemotherapy should be avoided in patients who already have preexisting neuropathy.

Determining the functional status of an elderly patient by Eastern Cooperative Oncology Group (ECOG) or Karnofsky score is not sufficient. Additional assessment tools such as activities of daily living (ADL) and instrumental activities of daily living (IADL) are routinely used by geriatricians. Frailty assessment of the elderly population can predict those at risk for weight loss, weakness, slowness, poor energy, and low physical activity.[5] Other validated tools such as the Charlson age-comorbidity combined risk score, which takes into account the number and significance of comorbid conditions, and the comprehensive geriatric assessment (includes physical and functional assessment, as well as social, psychologic, and environmental factors) may be utilized.[6] A cohort study of 5,330 older patients (median age 76 years) with stage III colon cancer from the Surveillance Epidemiology and End Results (SEER)-Medicare database analyzed the effect of chronic illnesses such as congestive heart failure, diabetes, and chronic obstructive pulmonary disease (COPD) and the use and effectiveness of adjuvant therapy.[7] Patients with heart failure received substantially less therapy, adjusted odds ratio 0.49 (95% CI, 0.40 to 0.60) when compared with those with diabetes 0.81 (95% CI, 0.68 to 0.97) and COPD 0.83 (95% CI, 0.70 to 0.99). Interestingly, the relative risk reduction in mortality associated with chemotherapy was similar in patients with and without heart failure.

Other factors to consider in elderly patients are their social support, psychology, and personal preference. Whether patients live alone or with family or friends, and if they are able to drive can greatly affect whether they will choose to receive chemotherapy. Elderly patients who have compromised mobility and/or cognition are very dependent on their social support to receive their chemotherapy and to manage their side effects in a safe and timely fashion. Also, the patient's personal preference of quality compared with length of life may also affect their decision to undergo adjuvant chemotherapy.

KEY POINTS

- Older patients as a population are undertreated in the adjuvant setting.
- There is a paucity of clinical trials in this patient population.
- Elderly patients differ in physiology, pharmacology, psychology, pathology, and personal preferences from their younger counterparts.
- Older patients may have increased toxicities from chemotherapy.
- Patients over age 70 do have survival benefit with adjuvant chemotherapy.
- Many older patients likely do not benefit from the addition of oxaliplatin to 5-fluorouracil.

ADJUVANT CHEMOTHERAPY

5-FU

Adjuvant chemotherapy with single-agent 5-FU has been shown to reduce the rate of recurrence and improve survival in selected patients with stage II and most with III colon cancer.[8,9]A pooled analysis of seven phase III randomized trials with stage II and III cancers in which patients were treated with either 5-FU and leucovorin or 5-FU and levamisole, analyzed 3,351 patients and showed that adjuvant therapy had a positive effect on overall survival (OS) and time to recurrence (TTR). The 5–year survival was improved from 64% to 71% with the addition of adjuvant chemotherapy, and there was only increased leucopenia in the older than 70 age group in one trial (5-FU and levamisole).[10] Thus, 5-FU appears to be well-tolerated in the elderly population, and treatment is associated with an overall survival benefit.

5-FU Compared with FOLFOX

Goldberg and colleagues performed a retrospective analysis of 3,742 elderly patients with either stage II, III, or IV colon cancer who were treated with bimonthly FOLFOX (oxaliplatin, 5-FU, and leucovorin) to examine safety and efficacy.[11] It is significant to point out that greater than 90% of the patients analyzed had performance status of 0 to 1. There was more grade 3 or higher hematologic toxicity and thrombocytopenia in older patients. There was no increase in severe neurologic side effects, diarrhea, infection, or nausea/vomiting. Age did not affect the response or recurrence rates, or survival. The landmark MOSAIC (Multi-center International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial randomly assigned 2,246 patients with stage II or III colon cancer to receive adjuvant 5-FU or 5-FU and oxaliplatin (FOLFOX) for 6 months, and results showed that there was a disease-free survival rate of 78.2% compared with 72.9% in the FOLFOX compared with 5-FU group, which was significant ($p = 0.002$).[12] Subgroup analysis of the 315 enrolled elderly patients (ages 70 to 75) found that the hazard ratio (HR) comparing FOLFOX to 5-FU was 0.93 (95% CI, 0.64 to 1.35) for disease-free survival (DFS) and 1.10 (95% CI, 0.73 to 1.65) for OS.[13] Also, patients had to have a Karnofsky performance status score of 60 to be eligible for the trial. However, the investigators recognized that elderly patients were a small subset and that the study was not powered for subgroup analysis. Also 40% of the elderly patients had stage II disease, and the subgroup analysis of stage II cancers showed that oxaliplatin also added little benefit to 5-FU.

The other important adjuvant oxaliplatin-based colon cancer trial was National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07, in which 2,409 patients with stage II and III disease were randomized to bolus 5-FU or bolus 5-FU and oxaliplatin.[14] Eighteen percent of the patients age 70 or older had an Eastern Cooperative Oncology Group (ECOG) performance score of 1 to 2. OS varied by age (<70 years vs. ≥ 70 years), and although oxaliplatin significantly improved OS in the younger population, the same benefit was not seen for the older patients ($p = 0.039$). In the older patients, OS at

4 years was 4.7% worse (71.6% vs. 76.3%) for the patients treated with bolus 5-FU and oxaliplatin when compared with bolus 5-FU alone, and there were higher rates of grade 4 and 5 toxicities (20% vs. 13%, respectively). It is possible that the bolus delivery of 5-FU in combination with oxaliplatin accounted for the increased toxicities.

In contrast to these two trials, analysis of N016968, a phase III trial of capecitabine and oxaliplatin compared with bolus 5-FU for stage III colon cancer showed improvement in DFS in both the younger than age 65 and age 65 and older patients with the combination treatment arm.[15] In the subgroup analysis of disease-free survival, HR for the combination arm compared with bolus 5-FU was 0.8 (95% for the younger population and for the older population. In multivariate analysis, age had a HR of 1.07 (95% CI, 0.99 to 1.15, $p = 0.0819$) for DFS and HR of 1.17 (95% CI 1.06 to 1.28, $p = 0.0016$). It is possible that the benefit seen was because only patients with stage III colon cancer enrolled in this trial. In contrast to the MOSAIC and C-07 trials that included patients with both stage II and III disease, and thus, discerned a greater benefit with the addition of oxaliplatin. Also, there could have been poorer tolerance to the bolus 5-FU compared with the combination therapy.

The ACCENT database of six phase III adjuvant trials (10,499 patients <70 years and 2,170 patients ≥ 70 years) of patients with stage II and III colon cancers was used to compare 5-FU to 5-FU combinations with oxaliplatin/irinotecan or capecitabine.[16] Combination chemotherapy and capecitabine did not lead to a significant improvement in survival outcome for the patients 70 years of age and older. In summary, subgroup analysis of phase III trials shows that elderly patients as a group may not benefit from the addition of oxaliplatin to 5-FU, although the numbers of older patients even in the meta-analyses are small and there are conflicting data with the N01698 trial showing results that are not consistent with MOSAIC and C-07. In addition, the elderly patients accrued in the trials had better performance status (Karnofsky 60 or better and ECOG 1 or better) than most elderly patients treated in the community.

Stage III

There are also population-database and retrospective studies that have looked at elderly populations to see which adjuvant chemotherapies benefit patients with stage III colon cancer the most. Sanoff and colleagues examined five observational databases and compared 4,060 patients who had oxaliplatin compared with nonoxaliplatin containing chemotherapy regimens.[17] It was noted that the choice to add oxaliplatin was inversely related to advancing age and that only half of the people in the older population received oxaliplatin-containing therapy. Patients in one elderly cohort (70 to 74 years) had a trend toward improved survival, although a different elderly cohort did not show improvement in survival, but there was no indication that adding oxaliplatin was harmful. A separate observational study of 675 older patients with stage III colon cancer examined the use of adjuvant chemotherapy and related side effects.[18] Age was associated with whether chemotherapy was received—50% of patients who were 75 years or older received chemotherapy, whereas 87% patients younger than 75 years received treatment. Older patients were more likely to discontinue therapy: 40% of patients 65 years and older discontinued therapy by day 150, whereas 25% of patients who were younger than 65 years stopped therapy. There were, however, lower adjusted rates of late clinical adverse events in patients who were 75 years or older. The authors concluded that older patients received shorter and less toxic chemotherapy regimens, as perhaps they should, based on careful management, to balance toxicity with treatment benefit. Sanoff and colleagues examined the effect of adjuvant therapy compared with surgery alone in another database analysis of 5,489 patients older than 75 years.[19] Results showed that the elderly population did have a survival benefit with chemotherapy, HR 0.60 (95% CI, 0.53 to 0.68). The addition of oxaliplatin, however, only offered a small benefit—5% absolute improvement in survival at 3 years.

TUMOR BIOLOGY

The tumor biology of colon cancer in young patients may differ from that of elderly patients. There are known different oncogenic drivers of colon cancer, including microsatellite instability (MSI), CpG island methylator phenotype (CIMP), and loss of heterozygosity (LOH, also known as chromosomal instability).[20] MSI tumors account for 15% of colon cancers and are divided into tumors with germ-line mutation of mismatch repair proteins caused by Lynch syndrome and sporadic hypermethylation (thus silencing) of the mismatch repair proteins caused by CIMP. Patients with Lynch syndrome are diagnosed at a much younger age, and CIMP tumors are more common in elderly patients and have a higher rate of *KRAS* or *BRAF* mutations.[21] Tumors with LOH account for 45% of colon cancer tumors and are found to be distinct from CIMP tumors. The presence of LOH is inversely related to the degree of methylation in CIMP tumors.[20] As we continue to dissect and characterize the molecular heterogeneity of colon cancers, we are able to identify patients with differential benefit from adjuvant chemotherapy. Sargent and colleagues correlated MSI status with survival and response to adjuvant infusional 5-FU in 456 patients with colon cancer and reported that patients with MSI tumors had better outcomes as compared with patients with microsatellite stable (MSS) tumors, but the improved prognosis was abrogated in the face of adjuvant 5-FU treatment.[22] We now routinely use MSI status to help us determine which patients with stage II colon cancer should not get adjuvant chemotherapy. MSI-H tumors have an excellent prognosis made worse by treatment and should be observed, not treated.

CONCLUSION

In summary, analyses of available data in older patients enrolled in adjuvant trials show that, as a group, they may not benefit from adjuvant chemotherapy regimens containing

oxaliplatin, or at least benefit as much, as younger patients. Although older patients do appear to benefit from adjuvant FOLFOX in stage III disease, as measured by DFS and OS, the benefit is less than that observed in younger patients. When evaluating a patient for adjuvant chemotherapy, practitioners should perform a comprehensive review of their performance status, comorbid medical conditions, medications, social support, and personal preference and consider using validated assessment tools. More data are needed on tumor biology as a function of age, as there are clearly signals that the biology of tumors that present in younger people differ from those that are diagnosed later in life. It is likely that some of the fit elderly will gain value from oxaliplatin-based regimens. In advising patients, clinicians should remember that the incremental benefit from 5FU-based adjuvant therapy overshadows the incremental benefit from adding oxaliplatin to those regimens, while avoiding long-term issues with peripheral neuropathy.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Relationships marked "U" are uncompensated.

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