

Adjuvant therapy for colon cancer in the elderly: treat or don't treat?

Jason S. Levitz, MD,¹ and Stuart M. Lichtman, MD²

¹Don Monti Division of Oncology, North Shore University Hospital, Manhasset, NY

²Memorial Sloan-Kettering Cancer Center at Suffolk, Commack, NY

The changing demographics of the population have emphasized the importance of the care of older cancer patients. Many recent advances have also occurred in the treatment of colon cancer, particularly in the role of adjuvant therapy. These changes have included the addition of new drugs and schedules and the increasing recognition that older patients benefit from adjuvant therapy. In facing a decision regarding which particular regimen to use in the older patient, clinicians must take into account individual patient needs, comorbidities, cognitive function, and social supports. This article will review the adjuvant regimens and how they can be applied to the treatment of older patients.

The incidence of colorectal cancer increases with age and doubles every 10 years after the age of 40. Colorectal cancer is a disease of the elderly, with 70% of patients being 75 years or older. (The median age at diagnosis for the years 1997–2001 was 72 years.¹) In the United States, the incidence of colorectal cancer is 35/100,000 individuals; thus, 1 in 20 people will suffer from this disease during their lifetime. Unfortunately, older patients are underrepresented in clinical trials, and, as a result, it can be difficult for the community oncologist to determine whether the benefits demonstrated in younger patients can be extrapolated to the older population.²

The care and treatment of elderly patients with colorectal cancer are among the great challenges clinical oncologists face today. Elderly patients commonly have concurrent illnesses or other medical difficulties that are perceived to exacerbate the side effects of adjuvant treatment. Consequently, elderly patients are often denied the possible benefits of chemotherapy. In the United States, the percentage of the population aged 65 and older is increasing at an unprecedented rate. By 2025, 20% of the population will be 65 or older, and by 2030, the population in the United States over the age of 65 is expected to double. Concomitant with this aging of the population, life-expectancy rates are also increasing. A 65-year-old woman today is projected to live another 20 years.

Aging is a highly individual process, and elderly patients form a heterogeneous population. Prognostic factors, such as the Eastern Cooperative Oncol-

ogy Group's (ECOG) performance status, which provide a useful guide in making treatment decisions for younger patients, are often insufficient to assess the overall status of elderly patients.³ Factors that need to be evaluated in elderly patients include functional status, comorbidity, and cognition. These issues make decisions regarding therapy difficult for

KEY POINTS

Age at diagnosis is the strongest determinant of receiving adjuvant chemotherapy for stage III colon cancer.

Elderly patients receive the same benefits from adjuvant therapy as do younger patients—and have about the same level of risk.

Fluorouracil toxicity in the elderly is more dependent on schedule, gender, and performance status than age.

First-line therapy with capecitabine alone appears to be safe and effective in patients who are not good candidates for combination therapy.

Age should not be a limiting factor for patients who might benefit from combination chemotherapy with oxaliplatin.

FOLFOX should be considered in older patients with adequate performance and functional status.

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Correspondence to: Stuart M. Lichtman, MD, Memorial Sloan-Kettering Cancer Center at Suffolk, 650 Commack Road, Commack, NY 11725; telephone: 631-623-4100; fax: 631-864-3827; e-mail: lichtmas@mskcc.org

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the practitioner. There are now sufficient data available to provide guidance regarding the use of adjuvant chemotherapy in elderly patients with colon cancer. This article will review the pertinent data.

Do elderly patients go onto clinical trials?

Clinical trials provide physicians and patients invaluable information regarding disease processes and outcomes. When the number of patients who entered clinical trials was compared with the estimated number of patients with cancer in each decade of age, the underrepresentation was striking: One study found that although 63% of people in the general population aged 65 or older had cancer, only 25% of patients in that age group were represented in clinical trials. More than 50% of children with cancer who are 5–9 years old are accrued to clinical trials sponsored by the National Cancer Institute (NCI), compared with less than 1% of adults 75–79 years of age. Among adults, those 80 years of age or older are least likely to be enrolled.²

A variety of factors have been proposed as potential explanations for the drop in accrual to clinical trials associated with advancing age. One such factor may be that physicians are not offering clinical trials to their elderly patients. Studies have reported that up to 50% of physicians did not offer clinical trials to older patients based on age alone.⁴ It has been reported that although physicians asked 51% of patients younger than age 65, only 35% of patients over age 65 were offered to participate in clinical trials.⁵ In most cases, physician bias stemmed from the assumption that older people cannot tolerate chemotherapy or that the benefits of therapy are not worth the risks in this population.

Additional biases include patient and physician expectations, poor social support, the existence of comorbidities, and the unwillingness of third

parties to pay for such participation in clinical trials.^{5,6} As an example of the effect of these issues on clinical trial accrual, the median age of patients enrolled in a recently completed trial of adjuvant oxaliplatin (Eloxatin), 5-fluorouracil (5-FU), and leucovorin (LV) in colorectal cancer was 61 years—more than a decade younger than the median age of the disease in the general population. This discrepancy highlights the information gap facing the practicing clinician.⁷

Do elderly patients receive adjuvant chemotherapy?

The need for postsurgical treatment is dictated primarily by the stage of the cancer. For patients with node-positive (stage III) disease, adjuvant treatment reduces the risk of death by up to one third, compared with surgery alone.^{8–10} The NCI states that patients with stage III disease who are unable to enter a clinical trial should be offered adjuvant therapy unless there are medical or psychosocial contraindications.¹¹ Unfortunately, older patients with stage III colon cancer are offered and receive adjuvant chemotherapy less frequently than younger patients.^{12–15} According to the NCI's Surveillance, Epidemiology, and End Results (SEER) registries, which include data on approximately 11% of the population, only 48% of patients aged 65–74 and 24% of those aged 80–84 received adjuvant therapy for node-positive colorectal cancer.¹⁴

Studies have confirmed that age at diagnosis directly correlates with the use of adjuvant chemotherapy. Age at diagnosis is the strongest determinant of receiving adjuvant chemotherapy for stage III colon cancer: 78% of patients aged 65–69, 74% of those aged 70–74, 58% of those aged 75–79, 34% of those aged 80–84, and 11% of those aged 85–89 received postoperative chemotherapy.^{12,16} The association between age and chemotherapy use remained statistically significant after

adjustments for all variables in a multiple logistic regression model. Treatment rates decline dramatically with chronological age, and because patients in their 70s, and even their 80s, have a reasonable life expectancy, further efforts are needed to ensure that elderly patients have the opportunity to make informed decisions regarding potentially curative therapy.^{12,16}

Do elderly patients benefit from adjuvant therapy?

In 2001, Sargent et al published an age-based, pooled analysis of data from randomized trials comparing adjuvant 5-FU-based regimens with no adjuvant chemotherapy for elderly patients with resected stage II or III colon cancer.¹⁷ Seven randomized studies, with over 3,000 patients enrolled, were identified, including 1,446 patients with stage II disease and 1,905 with stage III disease.

In the pooled analysis, overall survival was significantly longer for patients treated with 5-FU-based therapy than for patients who did not receive adjuvant treatment. Patients who had been treated with 5-FU plus LV or levamisole (Ergamisol) had a 7% absolute increase in 5-year overall survival and a 5-year recurrence-free rate of 69%, compared with 58% in untreated patients. More importantly, no significant interaction was observed between age and treatment effect for overall survival or freedom from tumor recurrence, regardless of how age was included in the analysis. Elderly patients had no higher rates of nausea or vomiting, stomatitis, or diarrhea than did younger patients. Although the incidence of leukopenia was significantly higher among those who received 5-FU plus levamisole, among those who received 5-FU plus leucovorin, the increase was not statistically significant.

These findings are consistent with other reports of no increased myelotoxicity in otherwise healthy elderly patients treated with chemotherapeu-

tic regimens that are considered moderately myelotoxic in younger patients. The apparent benefits of adjuvant chemotherapy were further confirmed in a population-based study.¹⁸ Patients aged 65 and older with node-positive colorectal cancer were identified using a database developed in 1993 by Potosky and colleagues that links files of cancer patients from the SEER registries with Medicare claims files.¹⁹ (It is estimated that approximately 14% of the American population with cancer is represented in these data, and prior research has shown that in the aggregate, patients in such registries are demographically representative of the general population.) A total of 4,962 patients over the age of 65 were included in the study. Overall, 52% of patients received 5-FU-based adjuvant therapy, and adjuvant treatment resulted in a significant improvement in survival. A hazard ratio of 0.66 between treated and untreated patients was observed—similar to that found in randomized, controlled trials among younger patients.

Iwashyna and Lamont also collected data from the SEER-Medicare registries to study the all-cause mortality of elderly Medicare beneficiaries with a history of stage III colon cancer.²⁰ A sample size of 3,357 patients over the age of 67 with histologically confirmed stage III adenocarcinoma of the colon were stratified by age, race, gender, marital status, and socioeconomic status and then compared in regard to overall survival.

Statistical analysis clearly demonstrated a survival benefit associated with adjuvant 5-FU therapy: 89.6% of patients who had received 5-FU were alive at 1 year after diagnosis, in contrast to 85.6% of matched patients who did not. At 5 years after diagnosis, 52.7% of the treated elderly population and 40.7% of matched untreated patients were still alive. Adjuvant treatment with 5-FU reduced the hazard of death by 27% across all 6 years of follow up. In addition, the

beneficial effect of adjuvant 5-FU on overall survival did not vary between patients in their 70s (hazard ratio, 0.73) and those in their 80s (hazard ratio, 0.78).

There is now a large pool of data confirming that elderly patients with resected colon cancer, who are in otherwise good health, have improved survival with adjuvant chemotherapy and tolerate treatment regimens as well as younger patients. However, it is important to note potential limitations to these data. The first concerns the applicability of these studies to the general population of older patients. Generally excluded from clinical trials due to age or comorbidities, elderly patients who are enrolled onto clinical trials are a select group with good performance status and cognition. Although many elderly patients in the community fit these characteristics, others may be in poor health or are living under socioeconomic conditions that may or may not affect the efficacy and tolerability of adjuvant therapy. Second, less than 1% of patients participating in clinical trials are over the age of 80. Therefore, care should be taken when treating octogenarians. Lastly, the benefits and risks of adjuvant therapy in frail elderly patients are not well known, suggesting that adjuvant treatment of this population should proceed with caution.²¹

Which adjuvant therapy to choose?

Fluorouracil chemotherapy, with or without LV, has been the adjuvant treatment approach for over 30 years. Recently, several newer chemotherapeutic drugs have demonstrated substantial improvements in disease-free and overall survival over those achieved with 5-FU ± LV. However, are these newer drugs appropriate to use in the elderly population?

Fluorouracil

Fluorouracil is an antimetabolite with highly variable pharmacokinetics

among different patients. Although age does not affect the clearance of 5-FU, gender does appear to have an influence. Women clear 5-FU significantly more slowly than men do, correlating with their having an approximately 15% lower activity of dihydropyrimidine dehydrogenase—the initial rate-limiting enzyme in the catabolism of 5-FU—than men have. This discrepancy correlates with the clinical observation that women suffer increased toxicity, specifically stomatitis and leukopenia, when treated with 5-FU.²²

Fluorouracil has been infused over numerous schedules with little difference in efficacy but substantial variation in toxicity, mostly in older patients with colorectal cancer. In a prospective evaluation of bolus administration of 5-FU/LV on 5 consecutive days every 4 weeks (Mayo Clinic regimen), patients over 70 years of age experienced more grade 3 or 4 mucositis than did younger patients.²² The Mayo Clinic regimen seems to be less tolerable than weekly bolus 5-FU (Roswell Park schedule). However, a retrospective study revealed that elderly patients gained similar benefits and had similar toxicities as younger patients when given infusional 5-FU versus bolus 5-FU therapy. Specifically, in both age groups, infusional 5-FU resulted in significantly increased response rates, overall survival, and disease progression-free survival compared with bolus 5-FU.²³ From these reports, it would seem that increased toxicity in the elderly is dependent on schedule, gender, and performance status. The Quick And Simple And Reliable (QUASAR): study of colorectal cancer treatment demonstrated an efficacious adjuvant bolus regimen using a lower LV dose in a somewhat older patient population (36% over 70 years).²⁴

Capecitabine

Capecitabine (Xeloda), an oral fluoropyrimidine, is metabolized by three enzymes (carboxylesterase, cytidine deaminase, and intratumoral thy-

midine phosphorylase) to 5-FU. Age, gender, body surface area, and hepatic dysfunction do not significantly affect its pharmacology. This drug is contraindicated in patients with severe renal impairment and should be used with caution in the presence of renal insufficiency; however, it is widely used in the setting of both breast and colon cancers.

Capecitabine is generally well tolerated. A randomized phase III study compared monthly bolus 5-FU/LV with capecitabine as first-line treatment in patients with metastatic colorectal cancer. In terms of response, oral capecitabine was more active than 5-FU/LV.²⁵ Time to disease progression and survival were at least equivalent in the capecitabine and 5-FU/LV treatment arms, and the types of adverse reactions that occurred in patients receiving capecitabine were consistent with the known profiles of fluoropyrimidines in general.

However, the toxicity profile of capecitabine differed in several important respects from that of intravenous bolus 5-FU/LV. Compared with 5-FU/LV, capecitabine was associated with a substantially lower incidence of diarrhea, stomatitis, nausea, and alopecia. In addition, grade 3 or 4 stomatitis and neutropenic sepsis, as a consequence of rare neutropenia, were significantly less frequent among patients treated with capecitabine than among those given 5-FU/LV. In addition, capecitabine-treated patients had significantly fewer hospitalizations for the treatment of adverse events. Therefore, capecitabine demonstrated clinically meaningful benefits over bolus 5-FU/LV in terms of tolerability while achieving at least equivalent therapeutic benefits.

The relative superiority of capecitabine was further confirmed in a phase III study, known as the X-ACT (Xeloda in Adjuvant Colon Cancer Therapy) trial, comparing bolus 5-FU/LV (Mayo

Clinic regimen) with capecitabine in the adjuvant setting.²⁶ Patients receiving capecitabine experienced significantly less diarrhea, stomatitis, nausea, vomiting, alopecia, and neutropenia, although more experienced grade 3 hand-foot syndrome than those who were treated with bolus 5-FU/LV. Capecitabine demonstrated a similar, favorable safety profile in patients under age 65 and those aged 65 and older. Capecitabine was also superior to 5-FU/LV in disease-free and overall survival,²⁷ supported by superior relapse-free survival and safety, leading the X-ACT investigators to conclude that capecitabine should replace 5-FU/LV in the adjuvant therapy of colon cancer.

Capecitabine has also been studied as first-line therapy in older, less-fit patients with advanced colorectal cancer. Eligible patients had one or more of the following: age \geq 65 years, ECOG performance status \geq 1, an elevated lactate dehydrogenase level, prior pelvic radiation therapy, or liver enzyme abnormalities. Capecitabine, given as a low dose of 2,000 mg/m² on days 1–14 of a 21-day cycle, proved to be tolerable and active in these less-fit patients, demonstrating that single-agent therapy is effective in these understudied patients for whom combination chemotherapy may not be ideal.²⁸

Irinotecan

Irinotecan (Camptosar) is a topoisomerase I inhibitor approved for the treatment of metastatic colorectal cancer alone or in combination with 5-FU/LV. Administered to colorectal cancer patients either weekly or once every 3 weeks, irinotecan has shown similar efficacy and improvement in patient quality of life.²⁹

Patients over the age of 70, however, have more grade 3/4 diarrhea when given irinotecan weekly instead of once every 3 weeks.²⁹ Data from recent intergroup trials clearly demonstrate that bolus irinotecan in combination with 5-FU/LV should not be used as adjuvant therapy for

stage III colon cancer.³⁰

Oxaliplatin

Oxaliplatin is a platinum coordination complex with activity in colorectal cancer. Hematologic toxicity is moderate, but the most consistent side effect is a dose-related, transient peripheral neuropathy. Oxaliplatin differs from cisplatin in its lack of nephrotoxicity and from carboplatin (Paraplatin) in its mild hematologic toxicity.

One study examined the use of oxaliplatin with 5-FU/LV and found the combination to be feasible, safe, and effective in elderly colorectal cancer patients.³¹ In pretreated patients, some oxaliplatin toxicities (namely, thrombocytopenia and stomatitis) increased slightly with age, but the overall incidence of severe toxicity was similar to that reported in younger populations. Neurosensory toxicity did not worsen with age, and efficacy was maintained. The investigators therefore surmised that the risk/benefit ratio was maintained in elderly patients and concluded that age should not be a limiting factor for patients who might benefit from combination chemotherapy using oxaliplatin.

The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial was a large, randomized, multicenter, multinational phase III study whose primary endpoint was to demonstrate a 25% decrease in the risk of tumor recurrence at 3 years among patients with stage II/III colon cancer receiving infusional 5-FU/LV plus oxaliplatin.⁷ Over 2,000 patients with completely resected stage II or III colorectal cancer were randomly assigned to receive bolus followed by infusional 5-FU/LV (de Gramont regimen) or infusional 5-FU/LV plus oxaliplatin (FOLFOX) bimonthly for 12 cycles. The patients' median age was 60–61 years, and approximately a third were over age 65. Males slightly outnumbered females,

and all patients had a good performance status.

Results from this trial revealed a low (0.5%) mortality in both the FOLFOX and 5-FU/LV arms. Disease-free survival was significantly improved in the FOLFOX arm, with 78.2% (95% confidence interval [CI], 75.6%–80.7%) of patients surviving without recurrence at 3 years, compared with 72.9% (95% CI, 70.2%–75.7%) of those in the 5-FU/LV group ($P = 0.002$), which corresponds to a 23% reduction in the risk of relapse. However, the FOLFOX arm proved to be more toxic, with a 41% increase in the incidence of grade 3 or 4 neutropenia, but without a clinically significant increase in febrile neutropenia. Increases in grades 1, 2, and 3 neuropathy were also reported in the FOLFOX arm, but after 1 year, the incidence decreased to 1.1%. Although overall survival data are not yet available, the results from this trial have challenged the standard of care in adjuvant therapy of colorectal cancer. The FOLFOX regimen should be considered in older patients with adequate performance and functional status.

Oxaliplatin plus capecitabine

The Southern Italy Cooperative Oncology Group studied the use of oxaliplatin in combination with capecitabine (XELOX) in the elderly population.³² Patients 70 years or older with advanced colorectal cancer were treated with XELOX every 3 weeks; doses were escalated if no grade 2 or higher toxicity was reported in the previous cycle. A total of 33 patients ranging in age from 70 to 81 years (median age, 75 years) were enrolled; 8 patients were pretreated with adjuvant therapy, 19 were symptomatic, 18 had two or more sites of disease, and 13 had a previous loss of body weight.

Two patients receiving XELOX had a complete response, seven had partial responses, and five had a minor response, for an overall 42% response rate. All cases had a 50% or

more reduction of basal carcinoembryonic antigen (CEA) or cancer antigen (CA) 19.9 values. Only one patient receiving XELOX had grade 3 diarrhea, and four patients had grade 1 or 2 neuropathy with this regimen. The investigators therefore concluded that XELOX was safe and active in elderly patients with advanced colorectal cancer. The efficacy and safety of this regimen have also been demonstrated in a younger patient population (median age, 64 years).³³ There are no data now to support XELOX as an adjuvant regimen, but studies are ongoing to evaluate its efficacy in that setting.

Conclusion

Over the past 3 years, the therapy of colorectal cancer has changed dramatically, challenging community oncologists to find the best drug and combination for each of their patients. The evidence is growing that combinations of these newer agents not only have activity in elderly patients but also are safe and effective. It is now clear that elderly patients benefit from the use of adjuvant chemotherapy for stage III colorectal cancer.

Still, the clinician must make a determination whether to offer any adjuvant therapy to an elderly patient. An estimation of the patient's life expectancy must be made based on age, comorbidity, and functional status. An estimation of the toxicity of the available regimens must be calculated, and a clinical impression must be made of whether the patient can complete the proposed regimen. Only then should the regimen be prescribed. Currently, at least two Web sites are available that can assist in making treatment decisions for individual patients.^{33,34} Given their success in younger populations, it is imperative that these newer adjuvant therapy regimens be further evaluated in the elderly, including studies on patients who are frail and/or have decreased functional reserves.^{21,35–38}

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About the Authors

Affiliations: Jason S. Levitz, MD, is a fellow in the Don Monti Division of Oncology, North Shore University Hospital, Manhasset, NY. Stuart M. Lichtman, MD, is Associate Attending Physician in the Department of Medicine, Memorial Sloan-Kettering Cancer Center at Suffolk, Commack, NY.

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