Management of Advanced Colorectal Cancer in Older Patients

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Many elderly individuals have substantial life expectancy, even in the setting of significant illness. There is evidence to indicate that elderly individuals derive as much survival benefit as younger patients from standard chemotherapy approaches in advanced colorectal cancer. Effective treatments should not be withheld from older patients on the basis of age alone. Treatment decisions should be based on functional status, presence of comorbidities, and consideration of drug-specific toxicities that can be exacerbated in older individuals due to decreased functional reserve. Infusional and weekly fluorouracil (5-FU) regimens are better tolerated than bolus and monthly regimens. Oral capecitabine (Xeloda) reduces the frequency of a number of toxicities compared with bolus 5-FU, including stomatitis, a particularly debilitating toxicity in many elderly patients. The effectiveness and tolerability of oxaliplatin and irinotecan (Camptosar) appear to be similar in older and younger patients. Older patients can also receive bevacizumab (Avastin), although caution is warranted in those with cardiovascular disease. Overall survival in metastatic colorectal cancer improves with the availability of multiple effective chemotherapeutic agents. The full range of effective therapies in advanced colorectal cancer should be extended to elderly patients.

Approximately 70% of all cancer deaths are in persons aged 70 years or older. The US population is aging, such that it is estimated that 20% to 25% of the population will be 65 or older by 2025. Thus, there is likely to be an increasing number of older cancer patients in whom the goals of treatment, as in younger patients, are to prolong life and maintain quality of life. Life expectancy among older individuals is considerable, as shown for US women in Table 1.[1] A 75-year-old woman, for example, has a life expectancy of 12 years if she is healthy and would have a life expectancy of 7 years even if she had significant illness. In this regard, it is difficult to understand why older patients frequently are not represented in clinical trials of cancer therapies. Indeed, clinical trials of cancer therapies typically are performed in middle-aged patients with limited comorbidity; inclusion of older patients, who are more likely to have significant comorbidities, is minimal, and patients of any age with significant medical problems in addition to cancer are routinely excluded. In addition, most patients studied are Caucasian, and most studies are cancer center-based, reflecting patient populations with the wherewithal to receive treatment at such locales and failing to reflect populations and practices more common in the community setting.

Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Healthy</th>
<th>Average</th>
<th>Sick</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 yr</td>
<td>20.0 yr</td>
<td>18.5 yr</td>
<td>9.7 yr</td>
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<tr>
<td>70 yr</td>
<td>15.8 yr</td>
<td>14.8 yr</td>
<td>8.6 yr</td>
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<td>75 yr</td>
<td>12.1 yr</td>
<td>11.5 yr</td>
<td>7.3 yr</td>
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<tr>
<td>80 yr</td>
<td>8.8 yr</td>
<td>8.4 yr</td>
<td>5.9 yr</td>
</tr>
<tr>
<td>85 yr</td>
<td>6.1 yr</td>
<td>5.9 yr</td>
<td>4.5 yr</td>
</tr>
</tbody>
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Data from Extermann.[1]
whereas some are still working, showing underlying differences in functional status (eg, activities of
daily living) that can affect both treatment decisions and responses to treatment. With regard to the
impact of comorbidities in colorectal cancer per se, it has been found that comorbidity in early-stage
disease influences survival independent of the cancer.[2] Older patients usually have decreased
functional reserve that is particularly evident in responses to the toxicities of cancer therapies. Thus,
for example, grade 3 diarrhea in an 80-year-old patient might result in prolonged hospitalization with
no return to baseline function, whereas recovery from grade 3 or 4 diarrhea typically occurs much
more readily in a younger patient. Although grade 2 toxicities are frequently dismissed in discussions
of chemotherapy toxicity, grade 2 toxicities can be quite formidable in older patients due to
decreased functional reserve. Nevertheless, despite the complications attending treatment of older
patients, there is evidence indicating that they derive similar degrees of benefit from standard
treatments for colorectal cancer as do younger patients.[ 3,4] Although certain caveats apply to the
treatment of older patients, effective therapies should not be withheld from this population simply on
the basis of age. **Efficacy of 5-FU-Based Treatment** Current chemotherapy options in the
treatment of advanced colorectal cancer include fluoropyrimidines, consisting of fluorouracil (5-FU)
with or without leucovorin modulation and capecitabine (Xeloda), combination therapy with a
fluoropyrimidine plus oxaliplatin (Eloxatin) or irinotecan (Camptosar), and the potential addition of
biologic agents such as bevacizumab (Avastin) or cetuximab (Erbitux) to chemotherapy regimens. A
meta-analysis of outcomes in clinical trials of 5-FU/leucovorin adjuvant therapy in colorectal cancer
reported in 2001 indicated that there was no significant difference in benefit of adjuvant therapy vs
surgery alone in terms of overall and recurrencefree survival between patients ≤ 70 years and those
> 70 years (Figure 1).[3] In a trial reported several years ago, Popescu et al[4] found a small
difference in overall survival and no difference in failure-free survival between patients aged ≤ 70
years and those aged >70 years receiving primarily 5-FU-based palliative therapy for colorectal
cancer (Figure 1).
Figure 1: Effects of 5-FU–Based Treatment in Older vs Younger Colorectal Cancer Patients—(A) Overall and (B) recurrence-free survival in meta-analysis of adjuvant therapy trials reported by Sargent et al.[3] Reproduced, with permission, from Sargent.[3] (C1) Overall and (C2) failure-free survival in patients receiving palliative therapy in study by Popescu et al.[4] Reproduced, with permission, from Popescu.[4] (D1) Overall and (D2) progression-free survival in a pooled analysis reported by Folprecht et al.[5]; P = .01 for difference in progression-free survival. Reproduced, with permission, from Folprecht.[5]
More recently, a pooled retrospective analysis of source data from 3,825 patients receiving 5-FU-based treatment in 22 European trials in metastatic colorectal cancer identified 629 patients aged > 70 years.[5] Among both patients aged > 70 years and those aged ≤ 70 years, infusional 5-FU was associated with significantly increased response rates, overall survival, and progression-free survival compared with bolus 5-FU regimens. In total, response rates were similar in older and younger patients, there was no significant difference between the > 70 years and ≤ 70 years age groups with regard to overall survival, and there was a small but significant increase in progression-free survival among the older patients (Figure 1).[5] The conclusion of this analysis was that "fit" older patients (ie, those fit enough to be enrolled in clinical trials) benefited at least to the same extent from palliative 5-FU chemotherapy as did younger patients. **Toxicity of 5-FU-Based Treatment** In general, it is recognized that the addition of leucovorin modulation to 5-FU results in increased toxicity. Among the traditional regimens, the Roswell Park (weekly) 5-FU regimen is in general better tolerated than the Mayo Clinic (monthly) regimen. Analyses of these regimens indicate that age > 70 years and female gender are predictive of severe toxicity and treatment-related death. Available data support improved tolerability of infusional regimens compared with bolus regimens. Although much of the frequently cited literature indicates that older age is a risk factor for increased and more severe toxicity, it is important to note that this is somewhat dependent on the type of treatment given. For example, the Mayo regimen is often less well tolerated by older patients (eg, over the age of 70 to 75 years) due to problems with diarrhea and mucositis. The meta-analysis by Sargent et al[3] mentioned above showed that the frequency of grade 3 or worse leukopenia was increased significantly in patients aged > 70 years receiving adjuvant therapy for colorectal cancer (Figure 2).[3] Rates of stomatitis were nonsignificantly increased in older patients; however, stomatitis can be a devastating complication in the elderly, posing problems with nutrition, hydration, and quality of life. Avoidance of mucositis and stomatitis in this population is an important objective in management. **Newer Agents** The fluoropyrimidine capecitabine may be a particularly suitable alternative to 5-FU/leucovorin in older patients. In the X-ACT trial, adjuvant treatment with oral capecitabine was at least as effective in terms of progression-free survival as the Mayo 5-FU/leucovorin regimen.[6,7] Toxicities in the trial are shown in Figure 3. Capecitabine was associated with significantly reduced frequencies of stomatitis, diarrhea, neutropenia, nausea/ vomiting, and alopecia compared with 5-FU/leucovorin. The frequency of hand-foot syndrome was higher with capecitabine, but management of this adverse effect has become easier with continued experience with capecitabine. The appropriate dosage of capecitabine remains somewhat of an issue, with the full dosage of the agent (1,250 mg/m²) probably being infrequently used in clinical practice, especially among older patients. Comparative data on capecitabine vs infusional 5-FU, which tends to be better tolerated than bolus 5-FU, are still needed.
With regard to newer combinations, a recent observational review of the use of oxaliplatin/5-FU combinations in colorectal cancer has suggested little difference in efficacy or toxicity according to age ≤ 70 years or > 70 years (Figure 4).[8] Similarly, a study of capecitabine plus oxaliplatin as first-line therapy in metastatic colorectal cancer showed little difference in response rates according to age < 60 or ≤ 60 years, although this age split does not really capture what would be considered an elderly population.[9]

A GERCOR trial comparing the 5-FU/irinotecan combination FOLFIRI followed by the 5-FU/oxaliplatin combination FOLFOX6 vs the reverse sequence in patients aged a median of 61 to 65 years (oldest patient 75 years; again, not a truly elderly population) with metastatic disease showed no difference in progression-free survival between first-line FOLFOX6 and FOLFIRI and a small but significant difference favoring second-line FOLFOX6 (median 4.2 vs 2.5 months, \( P = .003 \).[10] Any of the above regimens may be considered alternatives in older patients. One caveat is that diarrhea with irinotecan can be troublesome, and thus may pose a particular problem in elderly patients. Specific data on newer combinations in elderly patients are available from a review of oxaliplatin and irinotecan combinations in patients aged 75 to 88 years with metastatic colorectal cancer.[11] The median age of patients in the study was 78 years; 41% of patients were receiving first-line chemotherapy, 51% second-line, and 8% third-line. Grade 3 or 4 toxicity occurred in 42% of patients, including neutropenia in 17%, diarrhea in 15%, neuropathy in 11%, nausea/vomiting in 8%, and thrombocytopenia in 6%. No difference in toxicity was observed according to age 75 to 79 years vs
≥ 80 years. Overall survival by age is shown in Figure 5, with the data suggesting a benefit of treatment in prolonging survival in these elderly patients.

It is important to note that a significant correlation has been observed between increased median overall survival and percentage of patient populations with the availability of three active drugs (5-FU/leucovorin, oxaliplatin, and irinotecan) in the treatment of advanced colorectal cancer (Figure 6).[12] The range of effective therapies should be made available to older patients, since their potential life expectancy warrants the best possible treatment.

The addition of such biologic agents as bevacizumab should be considered in older patients as well. An important consideration, however, is the association of bevacizumab treatment with thrombosis and hypertension. A recent trial of bevacizumab[13] in colorectal cancer patients excluded patients with significant atherosclerotic disease or other severe cardiovascular disease and those receiving anticoagulant therapy. These criteria would exclude many elderly patients in the community setting. Despite the exclusion of those with severe cardiovascular disease, there was a substantial frequency of hypertension in study patients, a finding that raises concerns regarding use in the elderly, of whom many have hypertension. It is somewhat reassuring that a recent report indicates that the agent can be used safely in patients receiving anticoagulant therapy. Overall, caution in use of the agent is warranted in patients with active coronary disease or other severe cardiovascular disease.

**Conclusions** A potential schema for treatment decisions for elderly patients based on performance and functional status and life expectancy is shown in Figure 7. Older patients with colorectal cancer who have adequate performance status and functional status and reasonable life expectancy should receive the same therapies as younger patients. These therapies include multiagent therapy, including the potential addition of bevacizumab. For those patients with poor performance status or poor functional status, single-agent therapy consisting of 5-FU/leucovorin or capecitabine should be considered, also with the potential addition of bevacizumab. Multiagent therapy may be considered in select patients on an individualized basis.
Figure 7: Schema—Treatment of older patients with metastatic colorectal cancer. 5-FU = fluorouracil; LV = leucovorin.

Disclosures:
Dr. Lichtman has served on speakers’ bureaus for Amgen, Ortho Biotech, GlaxoSmithKline, and Genentech.

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