Challenges in treating older cancer patients: colon cancer

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introduction
People over the age of 65 years comprise the fastest growing section of the population in western societies. This suggests that more people are likely to live long enough to develop cancer. The consequences of this are not only an anticipated increase in the overall cancer incidence, but also in the number of elderly cancer patients requiring treatment. In Europe and the USA over 60% of new cancer cases and over 70% of cancer deaths occur in those aged 65 years or older [1]. The number of adults in this age group is projected to double between now and 2030. Approximately 50% of colorectal cancer (CRC) patients are over 70 years of age with a median age at presentation of around 73 years and in this age group, CRC is the second most common cause of cancer death [2]. However, the relative survival of elderly (>65 years) CRC patients is generally worse than that of younger patients, possibly due to more advanced stage at presentation and also due to the fact that they may often receive suboptimal management [3–5].

The majority of patients with stage I or II CRC are cured by surgery alone, although a small percentage of patients with stage II disease may derive additional benefit from adjuvant therapy [6, 7]. The standard treatment for stage III colon cancer is surgery followed by adjuvant chemotherapy. Patients with metastases may benefit from systemic chemotherapy either alone or in combination with newer targeted agents, with surgical intervention where appropriate. Evidence from population-based studies has demonstrated that older patients are more often inadequately staged, undergo fewer elective operations [8] and are less likely to receive adjuvant chemotherapy and/or radiation than their younger counterparts [4, 9–12]. However, it could be argued that as elderly individuals are under-represented in clinical trials, the evidence basis for the inclusion of surgery, radiotherapy or chemotherapy alone or in combination in the management plan is rather weak [1, 13]. Indeed, the data appear especially sparse for patients aged 75 years or older. The reasons why elderly patients are less likely to be offered 'optimal treatment' include the fact that they are less likely to be referred to specialists, often due to concerns over their physical and mental frailty, and the fact that they are more likely to have comorbidities and age-specific deteriorating organ function, which could make their tolerance to chemotherapy more difficult to manage.

adjuvant chemotherapy
The use of adjuvant chemotherapy is aimed towards eradicating any residual micrometastatic disease following potentially curative surgery. However, the use of such treatment in patients >70 years of age remains controversial due to concerns over both toxicity and death due to causes not related to cancer.

A pooled analysis of 3351 patients with stage II/III colon cancer from seven studies, treated with 5-FU plus FA or levamisole, showed adjuvant treatment to have a statistically significant improvement on both overall survival and time to recurrence (P < 0.001 with hazard ratios [HRs] for death and recurrence of 0.76 and 0.68 respectively), when compared with surgery alone [14]. Furthermore, no significant interaction was observed between age and efficacy of treatment, and the incidence of toxicity was not increased in patients >70 years old except for leucopenia in one study. However, analysis of the four different age groups (<50 years; 51–60 years, 61–70 years and >70 years) showed the probability of death without recurrence of cancer to be strongly associated with age. Patients 50 years old or younger had a 2% chance of death unrelated to cancer whilst those >70 years had a 13% chance [14]. A population-based study, of 4768 stage III colon cancer patients ≥65 years, between 1992 and 1996, in which half the patients received adjuvant therapy, showed. 5-FU-based adjuvant therapy to be significantly associated with reduced mortality (HR for death was 0.66 [95% CI 0.60–0.73]) [12]. Another retrospective review of 85934 patients with stage III colon cancer, between 1990 and 2002, showed the use of adjuvant chemotherapy to be lower in the elderly, being 80%, 70% and 40% in patients <70 years, 70–79 years and >80 years, respectively [15]. However, adjuvant chemotherapy was shown to increase survival in the elderly in the same way as in younger patients.

The randomized X-ACT trial of adjuvant capcitabine versus bolus 5-FU/FA in patients with stage III colon cancer, and an upper age limit of 75 years (although patients up to 82 years were included), showed there to be no difference in terms of safety, for those patients <65 years and those ≥65 years [16]. It should be pointed out though, that specific guidelines for renal impairment should be applied when using capcitabine [17]. Nevertheless, a recent 5-year efficacy update from this trial presented at this year’s ASCO GI, showed age to be a significant factor on a multivariate analysis for overall.
survival [18]. UFT (oral uracil with tegafur plus FA) has also been shown to be equally effective with similar toxicity when compared with bolus 5-FU/FA in patients <60 and >60 years [19]. A retrospective review from the Royal Marsden Hospital, dealing with the use of adjuvant and palliative chemotherapy for the treatment of CRC in 310 patients 70 years or older, showed the elderly patients to experience more mucositis with the bolus regimen but no other differences in toxicity [20]. In the MOTAIC study of adjuvant FOLFOX4 versus infusional 5-FU/FA, both younger and older patients (>70 years of age but <75 years) received benefit from FOLFOX4 [21]. When considering the above study, certain limitations need to be taken into consideration, including an eligibility of up to 75 years and the fact that these were patients deemed fit for entry into a clinical trial. In addition, it should be noted that no population-based studies with this regimen are as yet available and there is no information for patients >75 years. Thus, toxicity may not be a major issue for the fit, elderly colon cancer patient. Administering adjuvant chemotherapy for at least 5 months on the other hand may be important in terms of efficacy, as demonstrated by a study in colon cancer patients who were >65 years of age [9].

As stated previously, the survival gain in an older patient population is difficult to assess due to an increase in deaths from other causes. In a recent publication on the use of adjuvant chemotherapy mostly in patients with stage II disease from the Quasar Collaborative Group, it was argued that by age 80, adjuvant chemotherapy can only show a very small net benefit even with the highest estimate for treatment efficacy [22]. The conclusions of the study in relation to elderly CRC patients may potentially reflect insufficient statistical power to detect small survival gains in this subgroup; in addition, the benefit of chemotherapy may have been underestimated in view of the fact that a large proportion of patients received a weekly 5-fluorouracil schedule, which may not be as effective as the more familiar 4-weekly ‘Mayo’ regimen.

The multiple regimens available to consider (e.g. 5-FU/FA, capecitabine, FOLFOX) also make the decision making process more of a challenge. Therefore, it is difficult to recommend adjuvant therapy for all elderly patients. Although adjuvant therapy trials have included very few patients >80 years, the evidence for the elderly patient’s ability to tolerate chemotherapy in general suggests that age alone should not exclude any stage III colon cancer patient from consideration for adjuvant therapy. On the other hand, there are very little data for over 75 year-olds and at this point for this particular age group, age alone may well be a legitimate consideration. Most importantly, the therapeutic decisions with regard to the choice and duration of adjuvant therapy should be reached jointly by patient and physician, taking into account individual preferences and coexistent co-morbidities.

**treatment of metastatic disease**

The efficacy of 5-FU has been shown in the treatment of the elderly CRC cancer patient, in a small historical study versus best supportive care (BSC) [23], and in a detailed retrospective analysis of 22 phase II and III trials which identified 629 patients over 70 years of age [2]. The latter analysis showed that fit, elderly patients, with CRC, can benefit from 5-FU-based chemotherapy to the same extent as younger patients, and indicated that infusional regimens were more effective than bolus 5-FU regimens. In a retrospective review of treatment outcomes in the palliative setting, older and younger patients were shown to exhibit similar efficacy in terms of response, relapse-free survival and 1-year survival, but with a slight reduction in overall survival (P = .04) [20]. Univariate and multivariate analyses based on the individual data from 602 patients, included in two phase III trials of irinotecan therapy (one in the first line, the other in the second line setting), to determine predictive factors of survival in mCRC, showed irinotecan-based therapy to be independently associated with improved survival and age not to be a prognostic factor [24]. More recently, a multivariate analysis including treatment and age was performed using the data from the 5-FU/FA and 5-FU/FA/irinotecan arms of three randomized studies [25–27], conducted between 1996 and 2001 [28]. Patients were divided into two groups: elderly, (≥70 years, n = 249) and non-elderly (<70 years, n = 1010).

Overall, the toxicity was broadly similar for the elderly and non-elderly patients whilst the efficacy data suggested that elderly patients were as likely to benefit from 5-FU/FA/irinotecan therapy as younger patients. Meanwhile, a pooled safety and efficacy analysis of FOLFOX4 in elderly (>70 years) compared with younger patients with CRC in the adjuvant [6], first-line [29, 30] and second-line [31] settings showed FOLFOX4 to maintain its efficacy and safety ratio in selected elderly CRC patients [32]. In this analysis only 16% of the patients enrolled into the trials were >70 years old and the data for patients over the age of 80 years using this regimen are scant. It should also be borne in mind once more that all the above data were generated from elderly patients deemed fit to enter clinical trials. Nevertheless, it appears that with careful monitoring for toxicity and rapid intervention there is probably no reason why elderly patients should not receive either irinotecan-based or oxaliplatin-based therapy unless other contraindications for chemotherapy exist. Other combination therapy studies support this conclusion [32–34]. More recently, randomised data from studies specifically designed to assess the role of single agent versus combination chemotherapy in the elderly CRC patients have been reported in abstract form and give additional useful information on patterns of toxicity and efficacy in the metastatic setting [35, 36].

Limited data from studies of the two targeted therapies approved for use in the treatment of CRC, namely cetuximab [37, 38] and bevacizumab [39, 40], suggest that they are probably safe in an elderly population. However, bevacizumab, in particular, has a side-effect profile that includes hypertension (the most frequent side effect), proteinuria, thromboembolic events, bleeding, wound healing complications and bowel perforation which need careful consideration when treating elderly CRC patients. In particular arterial thrombembolic events following bevacizumab were more likely to occur in patients above 65 years of age or who had a previous history (>18%) of such events. No doubt, additional data are likely to accumulate in the next few months, particularly in relation to the
interesting concept of using single agent 5-FU or its oral analogues with bevacizumab in this patient population. The available data, although limited, suggest that cetuximab both alone and in combination is safe and active in "fit" elderly patients with CRC both first- and second-/subsequent-line, and that cetuximab monotherapy [41–44] might be an option for those patients who are not candidates for chemotherapy in either the first or subsequent-line settings. Clearly, more data are required. In patients with a mean age of 62 years, the anti-EGFR agent panitumumab has been shown to prolong PFS in previously treated mCRC patients [45]. The recently reported limitations in relation to K-ras mutated patients and monoclonal antibody EGFR-directed therapy should of course apply to the elderly as well.

Despite the recent advances in first-line chemotherapy strategies for the treatment of patients with advanced colorectal cancer (CRC), liver resection offers the only chance of long-term survival or even cure for patients with colorectal liver metastases. Over the past 5 years there has been the recognition that preoperative, neoadjuvant, combination chemotherapy regimens can facilitate the downsizing of colorectal liver metastases and render initially unresectable metastases resectable [46–50], and that the addition of targeted therapies [51–56] or a third cytotoxic to these standard combination therapy regimens [57–60] might render them even more effective in this clinical setting. However, almost no elderly patients have been included in trials of preoperative chemotherapy. Certainly the tolerance of the elderly patient to the triplet cytotoxic chemotherapy regimen that is emerging as one of the most active in this setting, is questionable and ought to be tested further. It should also be borne in mind that chemotherapy can be associated with increased postoperative morbidity, particularly after prolonged use [61, 62]. A recent retrospective report from the LiverMetSurvey registry suggests that well selected elderly patients may benefit from liver metastasectomy, with 5-year survival of about 37% [63]. Peri-operative mortality was increased though for this group of patients.

As a consequence of the under-representation of elderly patients in clinical trials and despite the fact that patients over 70 years of age represent half of all colorectal cancer patients, our knowledge of the performance of the appropriate therapeutic strategies in this age group is often very limited [64–68]. The low rate of inclusion, ranging from one quarter to one third of potentially eligible elderly patients in chemotherapy trials, can be due to a range of factors. The most common barriers reported in one literature review were physician's perceptions and protocol eligibility criteria (pre-determined subject age limits, restrictions on co-morbid conditions, and functional status requirements to optimize treatment tolerability). Other barriers were logistical, relating to the lack of social support for elderly patients and the extra time needed for patient enrolment. For similar reasons, this lack of access to treatment for eligible elderly patients presumably also extends to those treated outside clinical trials in community settings. It is fair to say that the Oncology Community has yet to conduct appropriate dose optimization trials in the elderly. Therefore we are currently ill-equipped to select appropriate doses with predictable and acceptable levels of toxicity for this group of patients. Efforts should therefore be concentrated toward designing innovative trials aimed specifically at the elderly CRC patients, so that the required evidence basis can become available to help us select the best treatment strategies.

disclosures

Demetris Papamichael has attended advisory boards and received honoraria from Merck-Serono and Pfizer. In addition he is currently conducting research sponsored by both companies.

references


36. Seymour MT, Maughan TS, Wasan HS et al. Capecitabine (Cap) and oxaliplatin (Ox) in elderly and/or frail patients with metastatic colorectal cancer: The FOCUS2 trial. J Clin Oncol 2007; (Abstract 9030).


