Mini-Review

Effect of Adjuvant Chemotherapy on Elderly Colorectal Cancer Patients: Lack of Evidence

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Keywords

Adjuvant chemotherapy · Aged patients · Colorectal neoplasms · Epidemiology · Oxaliplatin · Review

Abstract

Background: Adjuvant chemotherapy has become the standard form of treatment for all patients with stage III colorectal cancer and is also recommended for patients with stage II disease and defined risk factors. However, clinical studies that evaluate the effect of adjuvant treatment regimens have a selection bias in favor of younger patients, so that even retrospective subgroup analyses cannot define the best therapeutic procedure in elderly patients with comorbidities. **Summary:** As long as the role of adjuvant chemotherapy in elderly colorectal cancer patients is not investigated in comprehensive trials, no clear recommendations are possible. **Key Message:** An exploratory review of the relevant literature revealed that a formal meta-analysis concerning adjuvant chemotherapy in elderly patients with colorectal cancer is not feasible due to varying definitions of elderly patients, inclusion and exclusion criteria, and a plethora of chemotherapeutic regimens. **Practical Implications:** Given the high incidence of colorectal cancer and the median age of 68 years for patients at the time of diagnosis, health economic considerations should promote randomized controlled trials regarding the role of adjuvant chemotherapy in the elderly.

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The Clinical Problem

We live in a world of evidence-based medicine. However, most of our daily work is not evidence based. Small patient numbers of a specific disease group are often a limiting factor and the reason why no randomized controlled trials have been conducted. Colorectal cancer is occurring increasingly in the elderly population. The median age at the time of diagnosis is 68 years [1, 2]. However, there has been no randomized controlled study published regarding the specific effects of adjuvant chemotherapy in elderly patients. In fact, these patients are not even reflected in most clinical trials due to strict age-based inclusion and exclusion criteria.

Adjuvant chemotherapy is recommended for patients with stage III colorectal cancer, as well as for patients with stage II disease if they have a distinctive risk profile such as micro-satellite stability, tumor perforation, or <12 harvested lymph nodes, although data showing survival benefits for these risk groups are lacking [3–5]. Clear recommendations for specific regimens (i.e., mainly FOLFOX or CAPOX) have been established by large randomized clinical trials. However, no study exists that randomized for different age groups. Up to now, only retrospective studies with a putative selection bias or subgroup analyses are available, and it is not clear whether age is a predictive factor for the effectiveness of adjuvant chemotherapy [6]. Relevant issues include chronological and biological patient age together with comorbidities and individual performance status, putative stage-dependent different chemotherapy benefits for elderly opposed to younger patients, as well as appropriate regimens and applications (5-fluorouracil [5-FU]/capecitabine monotherapy or combinations with other substances such as oxaliplatin, capecitabine dose finding, bolus injection, FOLFOX6 vs. FOLFOX7). This review reflects the current evidence and opens questions regarding adjuvant chemotherapy in patients after resection of stage II or III colorectal cancer, with a special focus on elderly patients.

Adjuvant Chemotherapy for Resected Colorectal Cancer during the Last Decades

The survival of colorectal cancer patients has improved over the years due to surgical and medical therapeutic advances [7]. 5-FU was clinically introduced for colorectal cancer in 1985 [8]. Initially, it was given to patients with advanced disease in combination with levamisole, originally an anthelmintic drug, which was thought to augment the effect of 5-FU while at the same time reducing toxicity [9]. In the early 1990s, several studies (MOSAIC [10], NSABP C-07 [11], XELOXA (N016968) [12]) proved that 5-FU-based chemotherapy reduced subsequent mortality for patients with stage III colorectal cancer, thereby making it the standard treatment for these patients [9, 13]. Later, levamisole was replaced by folinic acid (Leucovorin® [LV]), which enhanced the 5-FU-dependent inhibition of thymidylate synthase by increasing the intracellular pool of folinic acid. Oral treatment became possible with the availability of capecitabine (Xeloda®), a prodrug of 5-FU [9]. Today's evidence suggests that the best effect is achieved with the addition of oxaliplatin in the adjuvant setting, leading to the so-called FOLFOX or XELOX regimens [9].

Definition of “Elderly Patients”

Ambiguity still exists regarding the most suitable adjuvant treatment of elderly patients. What makes things complicated is the classification “the elderly,” a term often used in publications, but never clearly defined. According to the WHO, patients older than 65 years are

defined as elderly [14]. However, most studies use 70 years [13, 15, 16] or 75 years [17, 18] as the cutoff point. Many clinical trials have age as exclusion criteria, which renders patients older than 70 years underrepresented in studies [9]. A more pragmatic approach to classifying could be by using tools for predicting chemotherapy toxicity in elderly patients [19] and functional status instead of the patient's chronological age. This can be assessed by functional performance scores such as comprehensive geriatric assessment [20], the Karnofsky index, the American Society of Anesthesiologists (ASA) score, or the Eastern Cooperative Oncology Group (ECOG) performance score [16]. Patients with an ECOG performance score of 3 or 4 or a Karnofsky index <60% are not considered candidates for chemotherapy, regardless of their age [16]. On the other hand, otherwise fit patients with stage III colon cancer and a life expectancy of >5 years might well be considered for adjuvant chemotherapy with 5-FU or capecitabine in combination with oxaliplatin, independent of their age [16].

The Pathophysiology of Aging

As a consequence of this idea, elderly patients could, in principle, have the same treatment as younger patients [16]. Rather than the chronological age, the biological status seems to play a role, including factors such as reduced organ function and functional resources of liver, kidneys, and bone marrow, a higher rate of cardiovascular risk factors, cognitive impairments, other comorbidities, and polypharmacy [16]. Patients 75 years of age or older have a median of five comorbidities at the time of their diagnosis, for instance cardiovascular conditions, chronic obstructive pulmonary disease, diabetes, previous cancer, renal failure, mental health disorders, obesity, Parkinson disease, or other organ dysfunctions [21]. These factors may contribute to a higher chemotherapy-specific toxicity in the elderly. Capecitabine is eliminated by the kidneys, which plays a role in the case of renal impairment [16]. Furthermore, 5-FU and capecitabine can cause coronary spasms, which may deteriorate coronary heart disease [16]. Higher rates of the so-called CpG island methylator phenotype and mutations in the genes p53, KRAS, and BRAF in elderly patients may also, at least in part, contribute to differences in the effect of adjuvant chemotherapy [16]. However, the impact of patient age itself is a matter of debate, as some studies describe better survival for elderly patients, whereas others have found advanced age as a nonprognostic factor or as a poor prognostic factor [2, 16].

Application Rate of Adjuvant Chemotherapy in Elderly Patients with Colorectal Cancer

Clearly, the rate of patients who are transferred to an oncologist postoperatively declines with rising patient age, as does the rate of patients who receive adjuvant chemotherapy after resection of stage III colorectal cancer [9, 13, 16, 22], despite data suggesting an oncological benefit for adjuvant treatment in elderly patients in general [9, 13]. Seventy-eight percent of patients between 65 and 69 years of age receive systemic treatment. The percentage decreases to 74% for the group between 70 and 74 years, to 58% for the group between 75 and 79 years, to 34% for the group between 80 and 84 years, and to 11% for the group between 85 and 89 years [6, 23]. There are online tools which estimate the recurrence risk for stage III colon cancer patients based on the data of large studies (e.g., <http://www.mayoclinic.org/medical-professionals/cancer-prediction-tools/colon-cancer>). These applications might be useful in the decision-making regarding adjuvant chemotherapy. They take into account the patient's age for a general risk assessment.

Adjuvant Treatment of Stage II Colorectal Cancer

Whether adjuvant chemotherapy is advantageous for patients with stage II (i.e., node-negative) colorectal cancer has been a matter of debate. The QUASAR trial [24] revealed improved survival for adjuvant 5-FU/LV in stage II patients, although the absolute improvement of 5-year overall survival was only 3.6% (95% CI 1.0–6.0; 84% with adjuvant chemotherapy versus 80% with surgery alone). Due to the limited benefit of 5-year overall survival for stage II colorectal cancer, compared to 60 versus 50% for stage III disease [25], the role of adjuvant systemic therapy for stage II colorectal cancer is still under controversial debate [3]. While 39% of all patients with colorectal cancer in the general population are older than 70 years [26], in the QUASAR trial [24] only 20% were 70 years of age or older (663 of 3,239). This suggests a reasonable selection bias, limiting especially the results of subgroup analyses by patient age. Of the 663 elderly patients in the trial, 331 received adjuvant chemotherapy, without a significant effect on the recurrence risk (RR 1.13; 95% CI 0.74–1.75). In contrast, the recurrence risk for the whole study population was significantly reduced by adjuvant chemotherapy (RR 0.78; 95% CI 0.64–0.95). The current International Society of Geriatric Oncology (SIOG) consensus recommendations [13] officially address the still existing controversy and lack of data for adjuvant chemotherapy in stage II colon cancer patients. Within the last years, molecular genetic markers have been increasingly used in clinical practice. Today, adjuvant 5-FU is recommended as an optional treatment for patients with stage II colon cancer and microsatellite stable tumors due to their reduced prognosis. On the other hand, it is not recommended for patients with microsatellite instable tumors, which are more likely to show resistance against 5-FU while harboring a more favorable intrinsic tumor biology also without adjuvant treatment [27]. Retrospective data suggest that these recommendations are transferable to elderly patients as well [28]. Although investigated in the MOSAIC trial [10], it is still not clear whether stage II patients profit more from FOLFOX or from 5-FU/LV [10]. Currently, 5-FU/LV or capecitabine is routinely applied in stage II patients and FOLFOX only in high-risk constellations or stage III disease, mainly directed by the profile of side effects [10].

Neoadjuvant and Adjuvant Treatment of Rectal Cancer

The treatment of rectal cancer differs in many ways from the treatment of colon cancer. After the first trials of the Gastrointestinal Tumor Study Group (GITSG) in the 1980s, adjuvant (postoperative) chemoradiation was introduced for locally advanced rectal cancer because it improved local control rate and survival [29, 30]. In the 2000s, a landmark trial by Sauer et al. [31] identified better local control and less toxicity for neoadjuvant chemoradiation compared to adjuvant chemoradiation, however with no improvement in overall survival. At the same time, the Stockholm II trial identified short-term preoperative radiation with 5 × 5 Gy to be similarly effective but less toxic than “long-term” chemoradiation especially in elderly patients [32]. Today, patients with rectal cancer who are fit enough to undergo resection are also considered fit enough to receive neoadjuvant (chemo-)radiation [16], which is recommended for cT3–4 or cN+ tumors [5]. Tolerance and response do not differ between younger and elderly patients; however, the postoperative 30-day mortality in patients older than 75 years is estimated to be higher after neoadjuvant radiation with 5 × 5 Gy compared to primary resection [16, 33].

Evidence from Large Randomized Controlled Trials

In a landmark analysis from 2001, Sargent et al. [34] pooled the data of 3,351 patients from 7 clinical studies (GIVIO [35], NCIC-CTG [36], FFCD [36], NCCTG [37, 38]/INT [39], SIENA [40], NCCTG [37, 38], and INT 0035 [39]) for the comparison of surgery alone versus adjuvant 5-FU-based chemotherapy for stage II and III colorectal cancer patients. Adjuvant chemotherapy led to an improved overall survival (HR for death 0.76, 95% CI 0.69–0.85, $p < 0.001$) and improved recurrence-free survival (HR for recurrence 0.68, 95% CI 0.60–0.76) for all patients, although without significant correlation between age and the effectiveness of treatment. Patient age had no influence on nausea, diarrhea, or stomatitis. Solely more leukopenia occurred within elderly patients ($p = 0.05$ for 5-FU/LV and $p = 0.001$ for 5-FU/levamisole). It has to be borne in mind that only 15% of patients in the pooled analysis of Sargent et al. [34] were over 75 years of age, and only 0.7% were over 80 years of age. Another pooled analysis [15] of 3,742 patients from four studies (MOSAIC [10], de Gramont [41], Goldberg [42], and Rothenberg [43]) investigated the association of adjuvant treatment with FOLFOX4 in the subgroups stage II and III colorectal cancer and patient age. Neither did patients younger or older than 70 years differ significantly regarding adverse effects (neurological, diarrhea, nausea, infections, $\geq$ grade 3 toxicity) nor regarding survival (recurrence-free survival, overall survival). In concordance with the analysis by Sargent et al. [34], only hematological toxicity $\geq$ grade 3 was increased in elderly patients (neutropenia: 49 vs. 43%, $p = 0.04$; thrombocytopenia: 5 vs. 2%, $p = 0.04$).

These pooled results from randomized controlled trials are in line with most other retrospective reports, which found improved survival for adjuvant 5-FU/LV or capecitabine in stage III colorectal cancer, regardless of patient age [16, 17, 22, 44, 45]. Some retrospective data describe a reduced effect of 5-FU-based chemotherapy with rising patient age [18]. However, the underlying cause of poorer outcome for elderly patients is not always well differentiated between the impact of chronological age and biological factors such as performance status or comorbidity [18]. A more recent retrospective analysis did not reveal an age effect influencing disease-free survival or mortality when adjusted for comorbidity in younger and elderly patients [46].

Adverse effects in general or specifically, for example mucositis, are reported to be slightly elevated in the elderly [45]. In addition, myelosuppression and fatigue appear to be age-specific complications [45]. Treating elderly patients with either 5-FU or capecitabine seems to have an adverse effect if they have impaired kidney function, which is a contraindication for capecitabine due to its renal elimination. Considering time to tumor recurrence, disease-free survival, and overall survival, a 2013 update of the ACCENT [47] database including seven adjuvant therapy trials did not reveal any differences between oral capecitabine or intravenous 5-FU/LV for younger patients versus patients older than 70 years [13, 47]. The currently recruiting ADAGE study's objective is to investigate different adjuvant regimens (5-FU/LV, capecitabine, FOLFOX4, XELOX, or observation) in elderly colon cancer patients in a randomized multicenter setting for the first time [48].

The Role of Oxaliplatin in the Elderly

Conflicting data for oxaliplatin in the elderly population exist. Since the MOSAIC trial [10], only FOLFOX is considered more effective than 5-FU/LV alone for stage III patients of any age. However, subgroup analyses of randomized controlled trials did not reveal a benefit of adding oxaliplatin to 5-FU-based chemotherapy for patients 70 years of age or older (disease-free survival: HR 0.94 [95% CI 0.78–1.13]; overall survival: HR 1.11 [95% CI 0.87–1.42]; time to

tumor recurrence: HR 1.35 [95% CI 1.04–1.76]; deaths within 6 months: 3.96 vs. 2.43%, $p = 0.3$) [10]. In concordance with this and an ACCENT database analysis [47], in the NSABP C-07 trial [11], no benefit could be shown for time to recurrence, disease-free survival, and overall survival in patients 70 years of age or older if oxaliplatin was added to 5-FU/LV. On the other hand, a pooled analysis of four studies (X-ACT [49], XELOXA [12], NSABP C-08 [50], AVANT [51]) found a benefit of addition of oxaliplatin to 5-FU/LV, regardless of patient age or comorbidity, albeit the oncological effect of adjuvant treatment was limited in general for patients older than 70 years [13, 52]. However, only 904 patients were 70 years of age or older, compared to 3,915 patients under 70 years, again limiting the validity of these results [52].

Considering all this information, the currently available data do not allow clear recommendations for the use of oxaliplatin in the adjuvant setting of colorectal cancer, regardless of patient age. Individual decisions considering estimated recurrence risk, life expectancy, expected side effects, and costs are still necessary [13]. The risks and benefits of oxaliplatin should be considered for otherwise fit patients who are evaluated as able to tolerate possible adverse effects and who have a life expectancy of at least 5 years after stage III colon cancer resection. The same applies for stage II high-risk patients and for stage II patients who are MSI-H, due to the reduced 5-FU effect in this group. The oxaliplatin-containing regimen of choice is FOLFOX6. If neutropenia or thrombocytopenia occurs, the 5-FU bolus should be omitted (modified FOLFOX7). For all other patients, 5-FU/LV or capecitabine monotherapy is the current standard treatment. Still the optimal dose and the specific effect of capecitabine for elderly patients is not clear [53].

In any case, the additional effect of oxaliplatin for patients 70 years of age and older is very limited, and the main effect arises from 5-FU monotherapy [13]. Besides FOLFOX, another standard regimen of adjuvant chemotherapy for patients with stage III colorectal cancer is XELOX. However, the use of both regimens again is of uncertain benefit in patients aged over 70 years [13]. For stage II, the benefit of adjuvant chemotherapy (5-FU/LV with or without oxaliplatin) remains unclear, independent of the patient's age [13]. Here, adjuvant chemotherapy does not have a significant influence on overall survival in general; FOLFOX only increases disease-free survival in high-risk patients [9, 10].

Adjuvant Regimens That Are Not Recommended

Irinotecan [54–56], bevacizumab [57], and cetuximab [58, 59] have not proved to be beneficial in the adjuvant setting in randomized trials, and their use is therefore not recommended.

Conclusion

Currently, no age restriction for adjuvant chemotherapy in colorectal cancer patients can be determined, as chronological patient age alone has no predictive value [17]. The use of oxaliplatin for elderly patients is still a matter of debate. It should be added or omitted on an individual basis [13, 15]. The conduction of a formal meta-analysis is not possible with the presently available data because elderly patients are often underrepresented in randomized trials. No distinct recommendations can be given until future trials start to omit age restrictions and selective reporting on the outcome of elderly patients. The present vast lack of data is embarrassing, and nonpharmacological triggered randomized clinical trials are urgently needed.

Statement of Ethics

Since all original data of this study have already been published in individual reports and no form of research was performed on living individuals, no ethics approval by the institutional review board was requested. No patients were directly involved for the purpose of this study, thus no patient consent statement was sought.

Disclosure Statement

All authors declare that there is nothing to disclose. They declare no conflicts of interest and no financial support.

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