Chemotherapy in elderly patients with colorectal cancer

C.-H. Köhne, A. Grothey, C. Bokemeyer, N. Bontke & M. Aapro

Departments of Hematology/Oncology. University Rostock, University Halle, University Tübingen, Germany. Institute Multidisciplinaire d'Oncologie, Clinique de Genolier, Genolier, Switzerland

Summary

Background Colorectal cancer is usually diagnosed in patients around 70 years of age. With a continuous increase in life expectancy we may expect a higher number of elderly patients in the future. Because patients above 70 or 75 years are often excluded there is uncertainty as to what extent systemic adjuvant and palliative treatment should be offered to elderly patients.

Methods We reviewed the available literature on adjuvant and metastatic colorectal cancer in order to identify reports on elderly patients treated within chemotherapy trials.

Results Only about 20% of patients entering clinical trials belong to the age group of over 70 years and represent the minority of the very fit patients. Compared to their younger counterparts 5-FU-based treatment appears to be equally effective and more toxic according to some reports. Data regarding raltitrexed, oral fluoropyrimidines, topoisomerase I inhibitors or DACH-platin derivatives are limited but suggest no age-specific differences in activity or toxicity.

Conclusions Elderly patients should not be excluded from clinical trials and studies in unfit elderly patients are warranted. Elderly patients need more attention regarding their functional, social and mental status. Fit elderly patients should be offered adjuvant or palliative chemotherapy.

Key words colorectal cancer chemotherapy elderly review

Introduction

Major advances have been achieved in the curative and palliative [1-3] treatment of patients with colorectal cancer. It is now generally accepted that node positive patients with colon cancer should be offered 5-FU-based adjuvant treatment which can reduce the risk of death after curative resection by approximately 30% [4]. There is no consensus about the value of adjuvant chemotherapy for node-negative colorectal cancer patients [5, 6].

High risk patients with rectal cancer are offered several types of combined approaches: post-operative chemo-/radiotherapy, pre-operative radio- or chemo-/radiotherapy and post-operative chemotherapy alone are options which have various levels of favour [7-9].

In metastatic disease systemic chemotherapy has been shown to be of clinical benefit for patients in terms of prolongation of survival, symptomatic improvement and quality of life [10]. The chemotherapeutic arsenal has been broadened by the introduction of new active compounds such as topoisomerase I inhibitors, diamino-cyclohexan (DACH) platin-derivates, and oral Fluoropyrimidines which either alone or in combination with other drugs may allow a more individual selection of active combinations in the future. The specific data are discussed later in this paper.

There is, however, uncertainty as to what extent systemic adjuvant or palliative chemotherapy should be offered to elderly patients with colorectal cancer. This fact is related to the unfortunate underrepresentation or even exclusion of fit elderly patients from clinical studies [11] and also to the total lack of studies on unfit elderly, who represent at least 50% of the geriatric population presenting to major hospitals [12].

The mean life expectancy of a 65-year-old man is approximately 13 years and statistically 11 of these are enjoyed without any physical handicaps. For a 65-year-old woman the mean life expectancy is estimated to be nearly 19 years of which 16 are enjoyed without physical handicaps [13]. Patients who have reached their 80th year still have a mean life expectancy of seven years for men and nine years for women [14]. Malignancies form the second cause of death after cardiovascular diseases in the age-group of over 65 years [15], and this age group represents more than half of all diagnosed cancers. Due to a decline in cardiovascular diseases accompanied with a continuous increase in life expectancy, we may expect a higher rate of elderly patients with malignant diseases in the future. WHO calculations lead us to believe that the number will double in the next 20 years [http://www.who.org/ageing/overview.html]. Very often these patients are not included in clinical trials, mainly because older age is chosen to be an exclusion criterion [16]. Among the relevant studies for the treatment of patients with colorectal cancer, probably no more than 20% of patients belong to the age-group of over 70 years.

There is a widely variable perception of the age at which a patient is considered elderly, and this is based on chronological rather than physiological age. In studies for the treatment of acute myeloid leukaemia patients...
over 60 are considered elderly [17] while patients with solid tumours have to be over 70 [18]. Due to the under-representation of elderly patients in clinical studies there is uncertainty as to what extent the results of these studies do apply to patients over 70 or even over 80 years of age. This is one of the reasons why elderly patients are less likely to receive effective therapy for their malignant disease compared to their younger counterparts [19]. According to a Dutch study [20] patients over the age of 70 had a three times lower probability of receiving any treatment (surgery, radiation or chemotherapy) for their malignant disease compared to patients under age 60. This survey included patients with breast, lung, ovarian, head and neck, colorectal cancer and malignant lymphoma.

According to a national data base report in the USA [21] only 24% of patients over the age of 70 received any additional therapy (radiotherapy or chemotherapy) following an operation, compared to 44% of patients under 60 years. For patients over 80 years of age radio-/ chemotherapy was used in only 8%.

The reason why elderly patients are less likely to be offered a specific treatment for their tumour is multifactorial. Advancing age is often associated with an increase in health problems including a decrease in cognitive and socio-economic abilities, a decline in organ functions and additional diseases. Cancer-specific treatment of elderly patients should therefore incorporate these factors. All these factors influence the survival of elderly patients with or without malignant disease. The functional status of patients and comorbidity have a weak correlation and comorbidity evaluation is of independent prognostic value, providing different information to classic performance status evaluation [22]. The use of comorbidity evaluation scales in oncology has not been standardised for individual patient care, and it remains a research tool. One reason is that the scales capture a quite different spectrum of factors [23]. The most frequent comorbidities of elderly patients when assessed with the Cumulative Illness Rating Scale-Geriatric (CIRS-G) are locomotive/tegumental problems (43%), vascular conditions (36%), genito-urinary diseases (31%), cardiac conditions (30%) and breast and endocrine diseases (29%). When using a different scale (Charlson), the most frequent diseases are secondary tumour (10%) and diabetes (7%). Geriatricians have also developed means to classify the functional status of patients taking into account their ability to cope with specific daily tasks [24]. These include daily body care, going shopping, doing telephone calls, having regular meals, be able to do small things in the household such as washing the laundry, retain mobility with public transportation, be able to take medication and also to take care of financial tasks. The use of such instruments along with evaluation of laboratory examinations and of mental status and potential depression constitute comprehensive geriatric assessments, which may help to better define populations that may or may not benefit from various therapeutic approaches [25].

Besides these socio-economic factors and comorbidities, changes in the elderly also occur in several organ functions. Noteworthy are alterations in kidney [26] and liver functions [27, 28] as well as the apparent bone marrow reserve [29, 30]. The glomerular filtration rate decreases and may alter the excretion of cytotoxic drugs, and because muscular mass tends to be decreased with age, normal serum creatinine may already reflect a decreased creatinine clearance, mandating the use of a correction of this value according to age with the formula of Cockcroft and Gault [31] for determination of the creatinine clearance. Drug metabolism may be altered due to a reduced hepatic blood flow, reduced albumine production and also a decrease in the cytochrome p450 function [28]. In addition, elderly patients very often have additional medication which may significantly influence the p450 cytochrome function.

Many cytotoxic drugs are myelotoxic and a higher haematological toxicity of different antineoplastic drugs has been observed in elderly patients. In addition elderly patients are more likely to suffer from neurotoxicity than younger patients. For this and other reasons clinicians often reduce the dose of cytotoxic drugs to lower the likelihood of their patients experiencing severe toxicity. However, dose reductions of conventional chemotherapy regimens [32, 33] may result in a less effective therapy. Therefore, if treatment has a curative intent, dose reductions of cytotoxic drugs may be deleterious.

Adjuvant chemotherapy for colorectal cancer in the elderly patient

Patients with newly diagnosed colorectal cancer have a median age of 70 years, while the median age of cohorts in clinical trials is usually 10 years less. Local recurrence or distant metastases are frequent within the first two years. An effective reduction in the occurrence of either a local or distant relapse may thus also be of major importance for patients over the age of 70 or 80, as their life expectancy largely exceeds the time in which appearance of metastatic disease would compromise their survival.

According to a survey in Germany [34] including 1001 patients of which 407 had Dukes C colon cancer and, thus, were candidates for adjuvant chemotherapy, only 62% received such treatment. One of the potential reasons why patients did not receive treatment was old age. While 69% of patients under the age of 70 were treated, only 47% of patients over 70 years received therapy. However, it is not known, whether age was the only reason to withhold therapy. It is also possible, that at least some of these older patients also had other comorbidities that were felt to make them unsuitable for chemotherapy. Recently, the value of adjuvant chemotherapy in elderly patients in stage II or III colon cancer was examined in a meta-analysis of seven studies including 3351 patients [35]. Five of these studies compared 5-FU-leucovorin and two compared 5-FU-levamisole to observation. The patient population consisted of patients with perfor-
mance status below or equal to 2 and chemotherapy started 21–56 days after surgery. Data on time to progression, survival and adverse events was available. All subjects were divided into four quartile-based age groups and elderly patients were considered to be above 70 years of age. As expected, death without cancer was more frequent in the elderly, occurring in 13% of 506 patients above 70 years and in only 1% of 564 patients below 50 years of age. Deaths without cancer were observed in 4% of the patients in the category of 51–60 years old \((n = 1012)\) and 7% in the category of 61 to 70 years old \((n = 1269)\). The benefit of adjuvant treatment was consistent across all age groups and no significant age-treatment interaction was observed. Therefore, the authors concluded that the benefit of treatment was not age-dependent.

Thus, the current information does not justify a separate study of adjuvant treatment of elderly patients compared to an untreated control, and elderly patients that are otherwise fit for chemotherapy should receive this treatment after resection of a high-risk colon or rectal cancer.

**Treatment of elderly patients with metastatic colorectal cancer**

Treatment of patients with metastatic disease is palliative. As for any other (age) group of patients, concern may be raised whether an elderly patient might benefit most from general supportive care rather than from toxic treatments. Beretta et al. have treated patients with a median age of 75 (range from 70 to 85 years) with best supportive care or a weekly 5-FU–folic acid regimen [36]. Interestingly, the median survival for patients receiving chemotherapy was prolonged by two months, indicating a potential benefit of chemotherapy in the elderly, confirming data from studies in the younger population.

Begg and Carbone [37] reviewed 19 different cancer trials from the Eastern Cooperative Oncology Group (ECOG), including 2 studies with colorectal cancer patients (Table 1). Among the 1208 patients with colorectal cancer 14% were over the age of 70. A survey was carried out in ECOG institutions to determine the prevalence of elderly patients attending oncology clinics generally. Not surprisingly a double percentage (28%) attended the clinics, indicating that a substantial number of patients were either not offered or were unsuitable to be included and treated within ECOG trials. Nevertheless, for those elderly patients that were included into clinical trials, the treatment was equally efficient when compared to younger patients. The objective response rate for patients under the age of 70 was 10%, and for patients over 70 years it was 9%. In addition, there was no survival difference observed for the two age categories (28 weeks). Similar analyses carried out within EORTC have confirmed these observations [11].

Stein et al. analysed a randomised trial conducted by the GITSG and reported in 1989 [38]. Patients received different 5-FU schedules modulated or not modulated with different doses of folic acid. The results of this trial were examined in the subgroups of patients younger or older than 70 years of age. The median survival for the younger group was 60 weeks and 41 weeks for the older group. The one-, two- and three-year estimated survival were 47%, 17% and 7%, respectively, for the younger, and 40%, 12% and 2% for the older patients \((P > 0.05)\). Differences in response rate etc. have not been reported.

Chiara et al. [39] examined two consecutive metastatic colorectal cancer trials conducted at the National Institute of Cancer Research in Genova. Elderly patients were defined as those of over 65 years of age. Out of 215 patients recruited, 82 patients with a median age of 70 years (range 65–77 years) were treated with different 5-FU bolus regimens or a weekly 24-hour infusion schedule. The overall objective response rate was 18% in the elderly group compared to 23% in the younger age group. Data on survival have not been reported.

Popescu et al. [40] analysed a large data base maintained at the Royal Marsden Hospital and identified 844 patients who had received first-line chemotherapy with various fluorouracil-containing regimens or raltitrexed for advanced disease. A total of 658 patients were below the age of 70, 112 were between 70 and 74 years, and 74 were above 75 years. The rate of objective response to first-line chemotherapy was 24% in 186 patients aged 70 or older, as compared to 29% in younger patients \((P = 0.19)\). There was also no statistically significant difference in failure-free survival or one year failure-free survival. However, the median overall survival time was shorter in the elderly group (292 vs. 390 days, \(P = 0.04\)). There were, however, more deaths due

---

**Table 1.** Response and survival following 5-FU-based chemotherapy according to retrospective studies in younger and older age groups.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Percentage ≥ 70 years</th>
<th>Response &lt; 70 years</th>
<th>Response ≥ 70 years</th>
<th>Survival &lt; 70 years</th>
<th>Survival ≥ 70 years</th>
<th>[Reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1208</td>
<td>14</td>
<td>10</td>
<td>9</td>
<td>28 weeks</td>
<td>28 weeks</td>
<td>[38]</td>
</tr>
<tr>
<td>331</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
<td>50 weeks</td>
<td>41 weeks</td>
<td>[39]</td>
</tr>
<tr>
<td>215</td>
<td>38</td>
<td>23</td>
<td>18</td>
<td>NA</td>
<td>NA</td>
<td>[40]</td>
</tr>
<tr>
<td>844</td>
<td>22</td>
<td>24</td>
<td>29</td>
<td>350 days</td>
<td>292 days</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* More deaths due to non-cancer causes.
to other than cancer causes in the elderly patient group, serving as a potential and plausible explanation for this observation.

Toxicity of 5-FU-based adjuvant chemotherapy treatment

Toxicity following adjuvant 5-FU-based treatment in elderly patients has been reported by three groups.

Brower et al. [41] examined 111 patients from Monroe County, New York, including a total of 45 patients over the age of 70. All received an adjuvant chemotherapy with 5-FU and levamisole after complete resection of colorectal cancer. The dose intensity delivered within the first 12 weeks was lower for patients of 75 years or older (71%) compared to patients of less than 70 years (84%). The rate of hospitalisation for treatment of drug toxicity was 35% for individuals of 75 years or older compared to only 8% for patients below 70 years of age. Not surprisingly, the drop-out rate was 35% for patients below 70 years and 53% for patients older or equal to 75 years.

In the Royal Marsden experience [40] half of the patients received either bolus or infusional 5-FU as adjuvant treatment. No statistically significant difference in the overall or severe toxicity between the population aged 70 or older or the younger cohort was observed. The only exception was stomatitis, which was more frequent in the older age group when all severe cases were considered (19% vs. 11%, P = 0.01). There was, however, no difference in stomatitis between the two age-groups, when only patients with infusional 5-FU were analysed. Infusional 5-FU was therefore recommended as the preferred mode of 5-FU administration for elderly patients.

In the large meta-analysis [35] on adjuvant treatment of elderly patients no clinically relevant toxicity differences were observed. In the subgroup of patients receiving 5-FU and Levamisole a higher incidence of leukopenia than or equal to grade 3 was observed for patients above the age of 70. This was not the case for 5-FU in combination with folic acid.

Toxicity of 5-FU-based treatment following palliative treatment

Renal elimination of 5-FU after reduction to dihydro-fluorouracil in the liver and mucosa is limited and estimated to account for not more than 10% of excreted 5-FU [42]. Therefore, 5-FU dose reduction in patients with renal dysfunction is usually not considered necessary. 5-FU is essentially cleared by hepatic metabolism. In a small study Floyd et al. [43] have reported that patients with clinically evident hepatic metastases showed lower 5-FU clearance and therefore recommended caution when giving 5-FU to patients with severe liver dysfunction. 5-FU-clearance is larger than predicted by hepatic blood flow. A large amount of 5-FU therefore has to be metabolised by extrahepatic tissue. Preliminary studies with a weekly 24-hour infusion in patients with renal and hepatic dysfunction [44] did not show alteration in 5-FU-clearance. Based on these pharmacological considerations and available clinical data, mild decrease in renal or hepatic function related to age is not a sufficient reason to reduce a 5-FU dose. Milano et al. [45] examined the potential influence of gender and age on fluorouracil clearance. Both factors are considered to have a potential implication in the pharmacokinetic variability of drugs. A total of 380 patients with head and neck cancer received cisplatin and a five day continuous infusion of 1 g/m² of 5-FU per day. Patients were divided into three age-groups (<50; 51-70; >70 years), with a significantly higher percentage of women older than 70 years compared to men (32% vs. 18%; P = 0.013). The influence of age and sex on the 5-FU-clearance was then analysed in a covariance analysis. There was no evidence that age modified 5-FU-clearance when it was adjusted for sex and dose. Thus female sex turned out to be a major determinant for increased toxicity, while age was not.

In a retrospective analysis on 331 patients treated within studies conducted by the Gastrointestinal Tumor Study Group [38], sex and age were identified as independent factors with a significant influence on toxicity of 5-FU-containing regimes. Sixty-seven individuals were over the age of seventy while two hundred sixty-four were younger. Severe toxicity of any kind was more likely to occur in the older age group (58% vs. 36%, P < 0.001). This was mainly due to severe leukopenia (10% vs. 24%, P = 0.005) and diarrhoea (14% vs. 24%, P < 0.01). However, patients in the older age group were also more likely to have more than two effected organ systems (3% vs. 10%, P = 0.02). Therefore, a higher tumour burden may also have contributed to the higher toxicity observed in some elderly patients.

The two ECOG trials mentioned earlier [37] used either a combination of 5-FU—cytoxane, 6TG, methyl-CCNU or 5-FU—methenyl-CCNU, vincristine, DTIC and hydroxyurea. Using these outdated treatment schedules no difference in haematological and gastrointestinal toxicity was observed in elderly and younger (<70 years) patients (Table 2).

The group from Genova [39] defined elderly patients as above 65 years. Younger and elderly patients received a 5-FU—folic acid-based treatment. The median dose intensity was similar for both age groups and no statistically significant differences in haematological or non-haematological toxicity's were observed between the two age groups.

Potential differences in toxic effects of 5-FU-based treatment were also analysed in the Royal Marsden data base [40]. When all grades of CTC-toxicity were considered, no statistically significant difference in haematological and non-haematological toxicity was observed for patients under or over the age of 70. There was, however, a trend for a higher rate of diarrhoea in the younger age group (50% vs. 43%, P = 0.09). Also nausea and vomiting of any grade was more frequent in
the younger patients (55% vs. 47%, P = 0.07). If only grade 3 and 4 CTC-toxicity's were analysed, no difference was observed in haematological and non-haematological toxicity's among younger or older patients. However, patients over the age of 70 received only 75% of the planned 5-FU dose intensity compared to 82% (P = 0.045) in the younger age group. Notably, the average length of inpatient stay by chemotherapy treatment for metastatic disease was 5.2 days in patients younger than 70 and 4.8 days for patients aged 70 years or older (P = 0.68).

**New drugs**

Recently the arsenal of effective antineoplastic agents for the treatment of colorectal cancer has been increased [46]. The place of compounds such as specific thymidilate synthase inhibitors, topoisomerase I interacting agents or oral fluoropyrimidines in the adjuvant or palliative treatment is still under investigation and for most of these their place has not been clearly defined. Nevertheless, they may become important in the near future in addition to 5-FU or may already represent treatment alternatives if 5-FU-based therapy is not desirable. The currently available information regarding efficacy and toxicity in elderly patients is reported here.

Raltitrexed is a specific thymidilate synthase inhibitor, 50% of which is excreted by the kidney. In case of renal dysfunction raltitrexed-clearance is reduced, possibly resulting in a higher drug toxicity. The dose of raltitrexed has to be adopted in these cases [47]. Raltitrexed was reported to be associated with a higher rate of toxic deaths in the Pan-European Trial on Adjuvant Colon Cancer (PETACC 1) which was therefore closed prematurely [48]. The higher rate of therapy-associated deaths may be due to several factors, among them a failure to adapt the raltitrexed dose in patients with renal dysfunction. A more detailed analysis of this adjuvant trial is awaited in order to more closely define the toxicity for the whole cohort, but also for elderly patients. Meanwhile, preliminary data of a British trial on the use of raltitrexed relative to different 5-FU schedules in patients with metastatic colorectal cancer has been published [49]. An unacceptable high rate of toxic deaths associated with raltitrexed was reported but detailed information is necessary. The use of raltitrexed may be justified in individuals with 5-FU-associated cardiotoxicity [50]. As older patients are more likely to have an underlying cardiovascular disease, and patients with pre-existing cardiovascular disease are probably more likely to experience 5-FU-associated cardiotoxicity [51], the use of raltitrexed in this age group may be of potential benefit. This hypothesis is supported by the observation by Zalcberg et al. [52], who reported on an age-dependant difference in toxicity following the Mayo Clinic Regimen (more toxicity in elderly patients) which was not observed for the use of raltitrexed. In a phase II study a Spanish Group [53] studied the efficacy and toxicity of raltitrexed in patients who were 70 years and older. According to the authors' perception the treatment with raltitrexed was associated with a low rate of toxicity and resulted in clinical improvement of tumour-associated symptoms in this age group of patients and was thus advocated for further investigation in elderly patients.

Pre-operative and post-operative radio-chemotherapy using raltitrexed has also been reported and appeared to be tolerable and effective [54, 55]. However, as long as we do not have a detailed toxicity analysis of the PETACC 1 study and of the separate English study that included patients with metastatic disease, 5-FU will remain the treatment of choice in the adjuvant treatment of elderly patients, when given alone or in combination with radiotherapy.

Recently developed oral fluoropyrimidines are 5-FU prodrugs and potential candidates to substitute 5-FU bolus or continuous infusion regimens [56]. UFT is a combination of tegafur and uracil in a molar ratio of 1:4. Two randomised trials for metastatic colorectal cancer demonstrated equal efficacy of UFT compared to a conventional 5-FU-bolus regimen, as well as less toxicity [57, 58]. Two Spanish groups reported good tolerability and efficacy for the use of UFT in elderly patients with metastatic colorectal cancer [59, 60].
addition, early phase II data for the combination of radio-chemotherapy with UFT are available [61]. Such a combination was feasible and down-staging was claimed in 50% of patients with rectal cancer. Nevertheless, the direct comparison of UFT and infusional regimens is pending and evidence on good tolerability, especially of UFT in combination with radiotherapy in elderly patients, is lacking.

The fluoropyrimidincarbamat capecitabine is also a 5-FU prodrug. The conversion to 5-FU needs three steps by hepatic carboxylesterase and cytidindeaminase. Over 70% of the metabolites are excreted by the kidney. Two randomised trials have concluded that capcitabine is at least as effective and is less toxic than a conventional modulated 5-FU bolus regimen [62, 63]. While capcitabine has been shown to be tolerated by fit elderly patients, information on dosing and scheduling for older patients with impaired organ functions is not available. A moderate restriction in liver function does not appear to alter the pharmacokinetics of this drug in a clinically relevant fashion [64].

The topoisomerase I inhibitor CPT-11 is a very promising compound for the treatment of 5-FU resistant [65, 66] and previously untreated patients and has been recently approved by health authorities for the treatment of metastatic colorectal cancer in combination with 5-FU. In two studies [67, 68] using either infusional or 5-FU bolus regimens, CPT-11 was able to improve the objective response rate as well as the median survival for patients receiving FU-FA plus CPT-11 combination. However, the inclusion criteria of both trials prevented patients of over 75 years to be treated within the protocol. The currently ongoing EORTC study 40986, which compares a weekly high dose infusional 5-FU regimen (AIO-schedule) with or without the addition of CPT-11, does not have an upper age limit. It appears that CPT-11 used as a single agent is associated with equal toxicity in younger and fit older patients (above 65 years of age) [69]. Additional pharmacokinetic studies have demonstrated equivalent drug pharmacological parameters for patients below or above 75 years of age [70]. In a phase II study patients 65 years or older were twice as likely (38.6% vs. 18.8%; P < 0.008) to develop grade 3–4 diarrhoea compared with younger patients when all courses of therapy were evaluated. However, older age did not significantly predict a higher incidence of first-course diarrhoea (25.0% vs. 14.7%; P = 0.106) [71]. The advice given that for patients over the age of 60 the dose of CPT-11 be reduced from 350 mg/m$^2$ to 300 mg/m$^2$ when given in a three-weekly schedule or from 125 mg/m$^2$ to 100 mg/m$^2$ in the weekly schedule, is rather a precaution than an evidence-based indication. Nevertheless, more data on the use of CPT-11 in elderly patients would be reassuring. Although the combination of CPT-11 with radiotherapy seems feasible [72], outside clinical trials, a combination with CPT-11 plus 5-FU plus radiation treatment is not justified in elderly and non-elderly population.

The diamnocylohexaneplatinum (DACH) oxaliplatin also has a high activity in combination with 5-FU in metastatic colorectal cancer [73] and has been recently approved by health authorities for the treatment of metastatic colorectal cancer in combination with 5-FU in some European countries. It can improve the efficacy of 5-FU-containing regimens according to the findings of randomised trials [74, 75]. In one randomised trial [74] accepting patients below the age of 75 years, the objective response rate was not different for a treatment with infusional 5-FU–leucovorin (22.2% vs. 21.4%) or infusional 5-FU–leucovorin plus oxaliplatin (50% vs. 50%) for elderly patients (> 65 years, n = 160) as compared to younger patients, respectively. Data on tolerability were also communicated in this study. In general, compared with younger patients this group of elderly patients did not experience increased toxicity except for grade 3–4 diarrhoea (18% vs. 8%, P = 0.34). However, both treatment arms were not evaluated separately, thus the toxicity of an oxaliplatin–5-FU combination in younger as compared to older patients remains unknown. Oxaliplatin’s characteristic toxicity is a cold-associated neurotoxicity as well as a cumulative neurotoxicity. In elderly patients with accompanying diabetes and possible diabetic neuropathy this could be a potential disadvantage. Electrophysiological examinations demonstrate that even a cumulative dose of 417 mg/m$^2$ may lead to sensory dysfunction [76].

Conclusions

Elderly patients are often excluded from clinical trials, and when included represent the minority of very fit elderly. Therefore, the data obtained from clinical trials have to be interpreted with caution as these results only apply to patients that fulfilled the protocol requirements. Nevertheless, the data clearly demonstrate that age alone is not a sufficient reason to withhold adjuvant or palliative treatment from an elderly patient. Age alone is also not a sufficient reason to reduce the dose of 5-FU or probably any other cytotoxic drug in patients with colorectal cancer. Nevertheless, the usual dose reduction schemes have to be followed for elderly as well as non-elderly patients. The performance status may be an insufficient mean to estimate the general condition of elderly patients and cofactors have to be considered. Elderly patients need more attention regarding their functional, social and mental status. In the future clinical trials should be open for all elderly patients, taking into account their different physiological profiles.

References

442


55 Valentini V, Morgante AG, Fiorentino S et al Chemoradiation with raltitrexed (Tomudex) and concomitant preoperative radiotherapy has potential in the treatment of stage II–III resectable rectal cancer. Proc Am Soc Clin Oncol 1999, 18


59 Dufz-Rubio E, Sastre J, Abad A et al UFT plus or minus calcium folinate for metastatic colorectal cancer in older patients. Oncology (Huntingt) 1999, 13 35–40


63 Twelves C, Shelygin YA, Burger HU et al A phase III trial (S01479E) of Xeloda™ (capecitabine) in previously untreated advanced/metastatic colorectal cancer. Proc Am Soc Clin Oncol 1999, 18


68 Saltz LB, Locker P, Pirota N et al Weekly irinotecan (CPT-11), fluorouracil (LV), and fluorouracil (FU) is superior to daily X 5 LV–FU in patients (pts) with previously untreated metastatic colorectal cancer (CRC). Proc Am Soc Clin Oncol 1999, 18 233a


Received 6 November 2000, accepted 22 December 2000

Correspondence to
PD Dr med C-H Köhne
University of Rostock
Clinic of Internal Medicine
Department of Hematology/Oncology
Ernst-Heydemann-Strasse 6
18057 Rostock
Germany
E-mail: henning.koehne@med.uni-rostock.de