Pergamon

European Journal of Cancer, Vol. 35, No. 12, pp. 1640–1649, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00185-9

Current Controversies in Cancer

Should Chemotherapy be Used as a Treatment of Advanced Colorectal Carcinoma (ACC) in Patients over 70 Years of Age?

B. Daniele P.D. Simmonds and L.Y. Best P.J. Ross and D. Cunningham

Pro:

B. Daniele

Division of Medical Oncology B, National Cancer Institute, via M. Semmola, 80131 Napoli, Italy

INTRODUCTION

CHEMOTHERAPY OF advanced solid tumours in the elderly has long been the subject of controversy. In most advanced cancers of the elderly the limited prolongation of survival, if any, induced by chemotherapy is balanced against the increased treatment toxicities which are usually observed in older patients. Another issue to take into account is the interaction of chemotherapy with the management of other comorbid illnesses often present in cancer patients of advanced age.

In this paper I summarise evidence available in the literature to try to support my opinion that generally favours the use of chemotherapy in this group of patients.

THE SIZE OF THE PROBLEM

Colorectal cancer is the second most common type of cancer after lung cancer in men and breast cancer in women [1]. In 1985, 678 000 new cases of colorectal cancer were diagnosed [2] and 394 000 patients died of the disease [3] worldwide. Approximately 70% of patients with colorectal cancer are over 65 years old [4] and, in Europe, approximately 40% are over 74 years old [5]. Thus, in the future the oncologist will face the question of whether to treat older patients with advanced colorectal cancer (ACC) with increasing frequency.

WHAT IS THE OUTCOME OF ELDERLY PATIENTS WITH COLORECTAL CANCER?

The recently published results of the EUROCARE II study on the survival of 701 521 European patients with colon and rectal cancers aged between 65 and 99 years indicate that in the years 1987–1989, survival of patients aged 65–74 years and of patients older that 74 years was lower than patients less than 65 years old, although survival had increased compared with the period of 1978–1980 [6]. This data confirms the findings of Arveaux and colleagues [7] who, in a population-based study of 2089 colon cancers, diagnosed in 1976 and 1990 in the French region of the Cote-D'Or, found a lower survival in patients older than 74 years.

Overall, these results indicate a worse prognosis for elderly patients with colorectal cancer. Besides the possible different natural history of colorectal cancer in the elderly, that, however, has not been substantiated by any evidence, the effect of age at diagnosis may affect the outcome by interfering, through performance status and comorbidities, with prevention, diagnosis and treatment.

EFFECT OF AGE ON THE TREATMENT OF COLORECTAL CANCER

In Europe, there is a trend toward therapeutic abstention in elderly patients with colorectal cancer. This holds true for surgery as well as for chemotherapy. The rate of surgery decreased from 85 to 73% in patients with colon cancer and from 85 to 70% in those with rectal cancer, but even more impressive was the drop in the number of patients treated with chemotherapy, from 11% in those younger than 65 years down to 1% in subjects older than 75 [8].

Moreover, anecdotal experiences suggest an empirical reduction of dosages in elderly patients. Generally, these data indicate that elderly patients with ACC are undertreated compared with younger subjects.

IS SURVIVAL OF PATIENTS WITH ACC INCREASED BY CHEMOTHERAPY?

Before discussing the specific issue of chemotherapy in elderly patients with ACC, it is useful to verify if chemotherapy is effective in increasing survival of younger patients with this disease.

Two studies compared systemic chemotherapy with no treatment in patients with ACC [9, 10]: both showed a better survival of patients receiving chemotherapy. On average, treatment added 5–6 months to the duration of survival.

E-mail: bdaniele@sirio-oncology.it

Table 1. *Bolus and continuous infusion (c.i.)* 5-*FU toxicities*

	Continuous infusion 5-FU (%)	Bolus 5-FU (%)
Grade 3–4 haematologiccal	4	31
Severe diarrhoea	4	6
Severe nausea/vomits	3	4
Severe mucositis	9	7
Hand–foot syndrome	34	13
Grade 3–4 non-haematological	13	14

Adapted from [13].

5-Fluorouracil (5-FU) has been the most widely used chemotherapy agent for treatment of colorectal cancer. The intravenous (i.v.) bolus administration of 5-FU was associated with a 10–15% response rate and a median survival of 6–9 months in metastatic colorectal cancer. The association of 5-FU with leucovorin showed a higher response rate compared with 5-FU alone, although no difference in survival was observed [11]. The modality of 5-FU administration also affects the results of treatment. A meta-analysis based on 1219 patients enrolled in 6 randomised trials showed that response rate and survival were better in patients receiving 5-FU by continuous infusion compared with bolus 5-FU (median survival 12.1 months compared with 11.3 months, $P = 0.04$) [12]. Moreover, 5-FU alone by i.v. bolus was clearly less effective than modulated 5-FU. Response rates were 10–15% for 5-FU alone and 20–25% for modulated 5-FU and continuous infusion 5-FU ($P = 0.0002$).

IS THE MODEST SURVIVAL ADVANTAGE WORTH THE TOXICITY OF CHEMOTHERAPY?

Due to the small survival advantage induced by chemotherapy, in the decision-making process it is important to take into account the toxicity profile of the treatment and its impact on quality of life in general and even more in elderly patients.

The toxicities of bolus and continuous infusion 5-FU are quite different, although generally mild [13]. Specifically, haematological toxicity is lower in patients treated with c.i. 5-FU, while the opposite holds true for the hand–foot syndrome (Table 1). In a meta-analysis of toxicities of 5-FU in patients with colorectal cancer, older age was an independent prognostic factor for non-haematological toxicity, mainly diarrhoea and mucositis, and the hand–foot syndrome [13].

However, there is evidence that prevention and treatment of these adverse affects can be achieved through a number of medications. Oral mucositis can be prevented by GM-CSF [14] and preliminary data suggest that the oral administration of the amino acid glutamine can reduce the duration and intensity of 5-FU-induced diarrhoea [15].

In the only study in which quality of life (QoL) was formally evaluated [10], chemotherapy did not induce a deterioration of QoL. Moreover the appearance of symptoms were delayed by chemotherapy [9] in asymptomatic subjects, and in 40% of patients receiving 5-FU-based chemotherapy the disappearance or a significant improvement of symptoms were observed, without severe adverse effects [16].

WHAT ARE THE RESULTS OF SPECIFIC TRIALS IN ELDERLY PATIENTS WITH ACC?

Few trials have been performed specifically in elderly patients with ACC. Most have been published only in abstract form and a few considered as elderly also patients aged 65–70 years. The most relevant studies have been summarised in Table 2.

Chemotherapy with weekly administration of 5-FU and folinic acid was compared with supportive care in patients $\geq$70 years old (range 70–85 years) [17]: treatment induced a survival advantage with a mild and reversible toxicity.

The effect of chemotherapy medications by the oral route has been investigated in the elderly due to its ease of administration. Falcone and colleagues [18] investigated oral doxifluridine in a phase II study on 43 patients older than 65 years with metastatic colorectal cancer. Median age was 74 years and all but 1 patient had not received previous chemotherapy. Treatment was well tolerated; diarrhoea was the most common side-effect (grade 3–4 in 17% of patients). Activity was moderate with a response rate of 14%.

Recently, the association of the oral fluoropyrimidine tegafur and leucovorin was investigated in 38 patients older than 70 years with ACC [19]. The overall response rate was 29%. Toxicity was mild and characterised by non-haematological side-effects, mainly diarrhoea (grade 3–4 in 10% of patients) and mucositis.

Chiara and colleagues, from the National Cancer Institute in Genoa, Italy, analysed the data relative to patients older than 65 years (median age 70 years) included in consecutive trials of 5-FU-based chemotherapy and compared them with the data of younger patients in the same trials [20]. No differences were observed in the median dose intensity administered and in toxicity between the two groups. The main side-effects in older patients were diarrhoea (38%), stomatitis (24%), hand–foot syndrome (13%) and haematological (15%). In the elderly versus younger patients there was no difference in overall objective response rates (18% versus 23%).

Table 2. *Studies of chemotherapy in elderly patients with advanced colorectal cancer*

Author [Ref.]	Drugs	No. pts	Median age (range)	Objective RR (%)	Major toxicities
Beretta [17]	FA + 5-FU i.v.	79	75 (70–85)	16.5	NA
Falcone [18]	Doxifluridine p.o.	43	74 (69–83)	14	Diarrhoea
Feliu [19]	tegafur p.o. + leucovorin	38	74 (70–81)	29	Diarrhoea Mucositis
Chiara [20]	5-FU-based i.v. chemotherapy	82	70 (65–77)	18	Diarrhoea Stomatitis Hand–foot syndrome

Pts, patients; RR, response rate; FA, folinic acid; 5-FU, 5-fluorouracil; NA, not available; i.v., intravenous; p.o., orally.

NEW DRUGS ACTIVE IN COLORECTAL CANCER

Irinotecan (CPT-11) is used for treatment of 5-FU-refractory colorectal cancer. No specific studies in the elderly are available, although patients up to 75 years old have been enrolled in few studies [21–23]. However, data extrapolated from different trials suggest that toxicity, namely diarrhoea, nausea and asthenia, becomes worse with increasing age ($\geq$65 years) [24, 25].

Tomudex (raltitrexed), a specific thymidylate synthase inhibitor, at a dose of 3 mg/m^2 every 21 days was administered to 116 patients >70 years [26]. Preliminary results indicate a 25% response rate and 45% stable disease with an acceptable toxicity profile. Major toxicities were diarrhoea (3% severe), fatigue and liver toxicity. These preliminary results are consistent with previous data indicating good tolerance of raltitrexed in patients with ACC older than 70 years enrolled in a phase III trial comparing raltitrexed with the association of leucovorin and 5-FU [27].

There is a lack of specific data regarding the use of oxaliplatin, a platinum compound active in ACC, in the elderly, although clinical trials included patients up to 75 years old [28, 29].

CONCLUSIONS

The studies with 5-FU-based chemotherapy in ACC indicate that treatment doubles patients survival, is not detrimental to their QoL and improves their symptoms. Based on these observations, I believe that patients older than 70 years should not be denied chemotherapy on the sole basis of chronologic age, unless specific controlled trials provide evidence to the contrary.

However, elderly patients do not age in a uniform way. Therefore, dedicated trials are needed to determine specific criteria that may help select those older patients that will likely benefit from chemotherapy. Another reason to perform such studies is that the goal of the treatment in older patients can be different compared with the younger ones. Namely, maintenance of good functional status and QoL may be prominent over a modest prolongation of survival.

QoL score at diagnosis, using the EORTC QLQ-C30 questionnaire, has been shown to be highly predictive of survival of elderly patients with advanced lung cancer, as well as of the number of chemotherapy cycles that they will receive [30]. Thus, the role of formal QoL assessment at diagnosis should be investigated in elderly patients with ACC.

In addition, a specific tool for the assessment of both functionality and performance in the elderly has been devised [31]. Its validity should be tested within controlled randomised trials as they may help to further define the population of elderly patients that can benefit from treatment.

Finally, the newer drugs active in colorectal cancer (raltitrexed, irinotecan, oxaliplatin) should be the subject of trials in the elderly to assess whether they can be added to the therapeutic armamentarium for older patients with ACC.

1. Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: cancer registry and estimates of national incidence for 1990. *Eur J Cancer* 1987, **33**, 1075–1107.
2. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. *Int J Cancer* 1993, **55**, 594–606.
3. Pisani P, Parkin DM, Ferlay J. Estimates of the worldwide mortality rate from 18 major cancers in 1985. Implications for prevention and projections of future burden. *Int J Cancer* 1993, **55**, 891–903.
4. Yankic R, Ries LA. Cancer in older persons: magnitude of the problem how do we apply what we know? *Cancer* 1994, **74**, 1995–2003.
5. Gatta G, Faivre J, Capocaccia R, Ponz de Leon M, the EUROCARE Working Group. Survival of colorectal cancer patients in Europe during the period 1978–1989. *Eur J Cancer* 1998, **34**, 2176–2183.
6. Vercelli M, Quaglia A, Casella C, *et al.* Relative survival in elderly cancer patients in Europe. *Eur J Cancer* 1998, **34**, 2264–2270.
7. Arveau I, Boutron MC, El Mrini T, *et al.* Colon cancer in the elderly: evidence for major improvements in health care and survival. *Br J Cancer* 1997, **76**, 963–967.
8. Gatta G, Sant M, Coebergh JW, Hakulinen T. Substantial variation in therapy for colorectal cancer across Europe: EUROCARE analysis of cancer registry data for 1987. *Eur J Cancer* 1996, **32A**, 831–835.
9. Nordic Gastrointestinal Tumour Adjuvant Therapy Group. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol* 1992, **10**, 904–911.
10. Schreithauer W, Rosen H, Korner GV, Sebesta C, Depisch D. Randomized comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *Br Med J* 1993, **306**, 752–755.
11. Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992, **10**, 896–903.
12. Meta-Analysis Group in Cancer. Efficacy of intravenous continuous infusion of 5-fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998, **16**, 301–308.
13. Meta-Analysis Group in Cancer. Toxicities of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. *J Clin Oncol* 1998, **16**, 3537–3541.
14. Chi KH, Chen CH, Chan WK, *et al.* Effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients after cisplatin, fluorouracil, and leucovorin chemotherapy. *J Clin Oncol* 1995, **13**, 2620–2628.
15. Daniele B, Perrone F, Pignata S, *et al.* Effect of oral glutamine on intestinal toxicity induced by 5-fluorouracil in patients with colorectal cancer: a double-blind, placebo-controlled trial. *Gastroenterology* 1999, **116**, A873.
16. Glimelius B. Biochemical modulation of 5-fluorouracil: a randomized comparison of sequential methotrexate, 5-fluorouracil and leucovorin versus sequential 5-fluorouracil and leucovorin in patients with advanced symptomatic colorectal cancer. *Ann Oncol* 1993, **43**, 235–240.
17. Beretta G, Bollina R, Cozzi C, Beretta GA, Morabito A. Should we consider the weekly (w) chemotherapy (CT) with fluorouracil (F) + racemic folinic acid (f) a standard treatment for advanced/metastaticcarcinoma of digestive tract (DTC) in elderly patients (pts?). *Proc Am Soc Clin Oncol* 1997, **16**, A920.
18. Falcone A, Pfanner E, Ricci S, *et al.* Oral doxifluridine in elderly patients with metastatic colorectal cancer: a multicenter phase 2 study. *Ann Oncol* 1994, **5**, 760–762.
19. Feliu J, Gonzàles Barón M, Espinosa E, *et al.* Uracil and tegafur modulated with leucovorin. An effective regimen with low toxicity for the treatment of colorectal carcinoma in the elderly. *Cancer* 1997, **79**, 1884–1889.
20. Chiara S, Nobile MT, Vincenti M, *et al.* Advanced colorectal cancer in the elderly: results of consecutive trials with 5-fluorouracil-based chemotherapy. *Cancer Chemother Pharmacol* 1998, **42**, 336–340.
21. Rougier P, Bugat R, Douillard JY, *et al.* Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. *J Clin Oncol* 1997, **15**, 251–260.

22. Cunningham D, Pyrhonen S, James RD, *et al*. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998, **352**, 1413–1418.
23. Rougier P, Van Cutsem E, Baietta E, *et al*. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998, **352**, 1407–1412.
24. Pazdur R, Zinner R, Rothenberg ML, *et al*. Age as a risk factor in irinotecan (CPT-11) treatment of 5-FU-refractory colorectal cancer. *Proc Am Soc Clin Oncol* 1997, **16**, A921.
25. Rothenberg ML, Cox JV, DeVore RF, *et al*. A multicenter, phase II trial of weekly irinotecan (CPT-11) in patients with previously treated colorectal carcinoma. *Cancer* 1999, **85**, 786–795.
26. Garcia De Paredes MM, Mel JR, Escudero PP, *et al*. An ongoing phase II study of tomudex (raltitrexed) in elderly patients with advanced colorectal cancer: an assessment of tolerability and clinical benefit. *Proc Am Soc Clin Oncol* 1999, **18**, A1092.
27. Zalcberg J, Kerr D, Seymour L, Palmer M. Haematological and non-haematological toxicity after 5-fluorouracil and leucovorin in patients with advanced colorectal cancer is significantly associated with gender, increasing age and cycle number. *Eur J Cancer* 1998, **34**, 1871–1875.
28. de Gramont A, Vignoud J, Tournigand C, *et al*. Oxaliplatin with high-dose leucovorin and 5-fluorouracil continuous infusion in pretreated metastatic colorectal cancer. *Eur J Cancer* 1997, **33**, 214–219.
29. Bécouarn Y, Ychou M, Ducreux M, *et al*. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. *J Clin Oncol* 1998, **16**, 2739–2744.
30. Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer. *J Natl Cancer Inst* 1999, **91**, 66–72.
31. Monfardini S, Ferrucci L, Fratino L. Validation of a multidimensional evaluation scale for use in elderly cancer patients. *Cancer* 1996, **77**, 395–401.

PII: S0959-8049(99)00188-4

Contra:

P.D. Simmonds L.Y. Best

CRC Wessex Medical Oncology Unit, Southampton General Hospital, Tremona Road, Southampton S016 6YD, U.K.

INTRODUCTION

COLORECTAL CANCER is predominantly a disease of the elderly, with over half of all deaths from this disease occurring in people over the age of 75 years [1]. Furthermore, the number of cases occurring in elderly people is expected to increase in the future as a result of population ageing. The primary treatment of colorectal cancer is surgical resection, but over half of all patients will eventually die of metastatic disease, which includes approximately 25% of patients who have evidence of metastases at the time of diagnosis [2].

Although the rate of progression of the disease is very variable, patients with advanced colorectal cancer have a median survival of only 6–9 months from the diagnosis of metastatic disease, during which time they may develop a wide variety of physical and psychological symptoms that detract from their quality of life and frequently precipitate hospital admission [3]. Since advanced colorectal cancer is usually incurable, the aims of treatment are prolongation of survival, effective symptom control and maintenance or improvement of quality of life (QoL). The adverse effects of chemotherapy must be weighed against any gain in survival, or improvement in cancer symptoms, a balance that will also be influenced by the choice of treatment and the expertise of the oncologist and supporting staff in selecting patients and managing side-effects [3]. In order to make such a judgement, these outcomes must be known for the patient group to which the treatment is to be offered.

Palliative chemotherapy is now offered to an increasing proportion of patients with advanced colorectal cancer due to recent advances which have resulted in increased response rates, a reduction in the side-effects of therapy and the demonstration of modest survival benefits, but there are good reasons to exercise caution in the use of this treatment in patients over 70 years of age.

WHY SHOULD ELDERLY PATIENTS BE CONSIDERED SEPARATELY?

Patients over 70 years of age form an extremely heterogeneous group as the cumulative effects of age-related physiological changes and comorbidities do not affect all individuals equally. Thus, the patient's physiological rather than chronological age should influence the choice of therapy. However, therapeutic decisions are often made on the basis of age alone, rather than more specific variables such as comorbidity, suitability for a particular type of intervention or the capacity to benefit [4, 5].

There is continuing uncertainty as to whether cancers behave more or less indolently in elderly individuals [6–9]. Age-related changes may alter the distribution and/or clearance of cytotoxic drugs in elderly patients [10–12], and the effectiveness of chemotherapy may be diminished and toxicity enhanced by pharmacodynamic changes [10, 11]. In some malignancies, the response to chemotherapy is lower and less durable among patients aged 60 years and over [13–15]. Molecular changes and changes in cell kinetics have been observed with a higher frequency in some tumours in elderly patients and may account for these differences [8, 10, 11, 16].

Predicting toxicity from chemotherapy is more difficult in elderly patients, in whom a combination of subtle defects in multiple organs may contribute to overall morbidity. Almost

Correspondence to P.D. Simmonds.