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CLINICAL TRIAL REPORT

**Silvana Chiara · Maria Teresa Nobile
Maura Vincenti · Rita Lionetto · Alberto Gozza
Maria Cristina Barzacchi · Ornella Sanguineti
Lazzaro Repetto · Riccardo Rosso**

Advanced colorectal cancer in the elderly: results of consecutive trials with 5-fluorouracil-based chemotherapy

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Abstract To evaluate toxicity and efficacy of chemotherapy in elderly patients (≥65 years of age) with advanced colorectal cancer, data from two consecutive trials conducted between 1984 and 1995 at the National Institute for Cancer Research were analysed comparing the results of treatment in those 65 years of age or older and in those younger than 65 years. Of 215 patients recruited, 82 elderly patients (median age 70 years, median performance status 1) received one of the following regimens based on 5-fluorouracil (5-FU): (1) weekly 5-FU 600 mg/m^2 i.v. bolus (30 patients); (2) weekly 5-FU 600 mg/m^2 bolus plus leucovorin (LV) 500 mg/m^2 2-h i.v. infusion (28 patients); (3) Weekly 5-FU 2600 mg/m^2 24-h continuous i.v. infusion plus LV 100 mg 4-h i.v. infusion and 50 mg orally every 4 h for five doses (24 patients). Overall, 1071 chemotherapy cycles were administered with a median number of 12 courses per patient. The main side effects were diarrhoea, observed in 38% of patients, stomatitis in 24% of patients and hand-foot syndrome in 13% of patients, and haematological toxicity affected only 15% of patients. No patient suffered grade IV toxicity. In three patients chemotherapy was discontinued because of toxicity (two patients suffered grade III diarrhoea, one patient grade III hand-foot syndrome). No significant difference in toxicity was evident between patients older than or younger than 65 years. Analysis of median dose intensity demonstrated no difference between the two groups. Overall objective response was observed in 18% (95% confidence limits 11–29) of elderly patients (15/82) in comparison with 23% (95% CL 17–32) of patients < 65 years of age (31/133 pts). In conclusion, chemotherapy in elderly patients with advanced colorectal cancer is a safe and effective treatment with acceptable toxicity and comparable objective response rates.

Key words Elderly · 5-Fluorouracil · Colorectal cancer · Toxicity · Activity

Introduction

Chemotherapeutic management of advanced colorectal cancer is a challenge to medical oncologists who have to treat elderly patients. Decisions based on age alone are inappropriate, but the risks versus benefits of therapy are still to be clarified.

The current treatment of both adjuvant and metastatic disease mainly involves the use of regimens based on 5-fluorouracil (5-FU). Biomodulation of 5-FU by leucovorin (LV) or methotrexate has led to a statistically significant increase in the response rate and a modest increase in median survival time compared with 5-FU alone [9–11]. Improvement in palliative effects has also been observed compared to supportive care alone [12]. However survival improvement has been only moderate, toxicity is frequent and severe, and the impact of chemotherapy on patients' quality of life has hardly been investigated. So physicians and their patients may reject conventional anticancer chemotherapy because of uncertainty about the therapeutic benefit and concern about the side effects.

The present study retrospectively analysed the toxicity and the activity of chemotherapy in 82 elderly patients (≥65 years of age) entered into consecutive trials conducted between 1984 and 1995 at the National Institute for Cancer Research [6, 7].

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S. Chiara (✉) · M.T. Nobile · M. Vincenti · A. Gozza
M.C. Barzacchi · O. Sanguineti · L. Repetto · R. Rosso
Department of Medical Oncology,
National Institute for Cancer Research,
V.le Rosanna Benzi, 10, 16132 Genova, Italy
Tel. +39-10-5600668; Fax +39-10-5600850

R. Lionetto
Epidemiologia Clinica e Sperimentazioni Cliniche Controllate,
Istituto Nazionale Ricerca Cancro,
V.le Rosanna Benzi, 10, 16132 Genova, Italy

Patients and methods

A total of 215 patients with advanced colorectal cancer entered two consecutive clinical trials. The first was a randomized comparison between weekly 5-FU alone and 5-FU plus LV, and the second was a phase II study with high-dose short-term continuous infusion (c.i.) of 5-FU. The regimens consisted of: (1) weekly 5-FU 600 mg/m^2 i.v. bolus (73 patients); (2) weekly LV 500 mg/m^2 by 2-h infusion, followed by 5-FU 600 mg/m^2 i.v. bolus (72 patients); (3) weekly LV 100 mg/m^2 by a 4-h infusion, followed by 5-FU 2600 mg/m^2 as a 24-h c.i., combined with oral LV 50 mg every 4 h for five doses (70 patients).

For both trials eligible patients had to have biopsy-proven, measurable metastatic colorectal cancer. Inclusion criteria were: ECOG performance status ≤2, age ≥18 years, and provision of informed written consent. Adequate haematological, renal and hepatic functions were required. Patients who had received previous chemotherapy for metastatic disease were excluded from the first randomized trial, but were included in the second phase II study.

Toxicity and objective responses were evaluated according to WHO criteria [4]. Dose intensity was calculated as mg/m^2 per week as suggested by Hryniuk and Bush [1]. The received dose intensities (RDI), i.e. dose or drug actually administered for unit of time, were calculated after 4 and 8 weeks of treatment.

This was a retrospective analysis of patients recruited into previous trials. The collected data provided the opportunity to describe and analyse the effects of age on treatment-related toxicity and on response rate, in order to generate a new hypothesis for future clinical studies. The study population was divided into 'younger' (age <65 years) and 'older' (age ≥65 years). The chi-squared test was used to explore the differences in specific organ toxicity between the patient groups. Data on response rates are expressed as the proportion of responders (complete response, partial response) in relation to all the other categories (minor response, stable disease, progressive disease and not evaluable). In order to assess the degree of confidence that the true proportions for success lay in the 95% interval, confidence limits were calculated, hypothesizing that both confidence intervals were almost superimposable.

Results

Patients' characteristics according to age (≥65 years versus <65 years) are shown in Table 1. The two groups were well balanced.

Overall 82 of the 215 patients were 65 years of age or more, and 1071 chemotherapy courses were administered with a median number of 12 cycles per patient (range 3–36). The elderly patients had a median age of 70 years (range 65–77 years) and a median performance status of (range 0–2). Of the 82 elderly patients, 40% had liver metastases and 10% had lung lesions; multiple metastatic sites were present in a larger proportion of patients (44%). Only ten patients had received previous chemotherapy for metastatic disease; all these patients were included in the phase II trial. In all cases first-line treatment included LV and 5-FU i.v. bolus.

The main toxicities in the elderly group were diarrhoea (in 38% of patients), stomatitis (in 24% of patients) and hand-foot syndrome (in 13% of patients). Haematological toxicity affected only 15% of patients (Table 2). No elderly patient suffered grade IV toxicity. No significant difference in toxicity was evident between patients older than and younger than 65 years.

Table 1 Characteristics of the 215 patients

	<65 years of age	≥65 years of age
Age (years)		
Median	58	70
Range	30–64	65–77
Performance status		
Median	1	1
Range	0–3	0–2
Sex		
Male	75	57
Female	58	25
Primary tumor		
Rectal	60	41
Colon	73	41
Site of metastasis		
Liver	68	33
Liver + others	18	29
Pelvis	4	1
Lung	12	8
Others	31	11
Regimen		
5-FU	43	30
5-FU + LV	44	28
High-dose 5-FU	46	24
Previous chemotherapy		
Yes	11	10
Number of administered courses		
Median	10	12
Range	2–39	3–36

In three patients chemotherapy was interrupted because of toxicity: two patients receiving the 5-FU and LV regimen suffered grade III diarrhoea, one patient treated with high-dose 24-h c.i. 5-FU had grade III hand-foot syndrome. Another patient refused therapy because of grade III stomatitis, experienced after three courses of the 5-FU and LV regimen.

Table 3 summarizes the toxicities according to chemotherapeutic regimen. The results confirmed previously reported data showing that bolus schedules produce more myelotoxicity, while c.i. schedules are complicated by stomatitis and dermatitis, mainly hand-food syndrome. The analysis showed that elderly patients did not experience more toxicity, whatever regimen they received.

Analysis of median dose intensity demonstrated no difference between patients older than and younger than 65 years. Patients treated with 5-FU received a median dose intensity of 600 mg/m^2 per week both at 4 weeks and at 8 weeks, patients treated with 5-FU + LV 600 mg/m^2 per week and 535 mg/m^2 per week at 4 and 8 weeks, respectively, and patients receiving high-dose c.i. 5-FU 2600 mg/m^2 per week and 2080 mg/m^2 per week at 4 and 8 weeks, respectively.

Overall objective response was observed in 18% (95% confidence limits 11–29) of elderly patients and in 23% (95% CL 17–32) of patients <65 years of age (Table 4). The objective responses according to

Table 2 Overall toxicity

	<65 years of age (133 patients)	≥65 years of age (82 patients)	*P*-value
Diarrhoea			
Grade 1–2	43 (32%)	16 (19%)	0.06
Grade 3–4	19 (14%)	15 (18%)	0.6
Stomatitis			
Grade 1–2	22 (16%)	16 (19%)	0.7
Grade 3–4	3 (2%)	4 (5%)	0.5
Cutaneous			
Grade 1–2	10 (7%)	2 (2%)	0.19
Grade 3–4	1 (1%)	–	0.6
Hand-foot syndrome			
Grade 1–2	20 (15%)	10 (12%)	0.7
Grade 3–4	4 (3%)	1 (1%)	0.7
Conjunctivitis	21 (16%)	15 (18%)	0.8
Nausea/vomiting			
Grade 1–2	55 (41%)	29 (35%)	0.5
Grade 3–4	5 (4%)	1 (1%)	0.5
Leukopenia			
Grade 1–2	12 (9%)	11 (13%)	0.4
Grade 3–4	–	1 (1%)	0.8
Thrombocytopenia			
Grade 1–2	5 (4%)	4 (5%)	0.8

chemotherapy regimen were 14%, 19% and 25% for 5-FU, 5-FU + LV and high-dose 5-FU, respectively, with no differences between the two patient groups (≥65 years and <65 years).

Discussion

In spite of the high proportion of cancer patients of advanced age, little is known about the impact of age on tumour biology or the morbidity associated with cancer treatment. Since advanced age is a common criterion for exclusion from clinical trials, little information is available on this category of patients.

The present retrospective analysis of 5-FU-based chemotherapy for metastatic colorectal cancer indicated that advanced age was neither associated with increased toxicity nor with reduced response rates. In particular, tolerance of treatment by elderly patients was similar to that by younger patients.

Table 3 Toxicity according to treatment

	5-FU		5-FU + LV		High-dose 5-FU	
	<65 years of age	≥65 years of age	<65 years of age	≥65 years of age	<65 years of age	≥65 years of age
Number of patients	43	30	44	28	46	24
Diarrhoea						
Grade 1–2	10	7	15	6	18	3
Grade 3–4	1	3	8	6	10	6
Stomatitis						
Grade 1–2	1	3	7	7	14	6
Grade 3–4	1	1	1	1	1	1
Cutaneous						
Grade 1–2	4	1	6	1	20	10
Grade 3–4	–	–	1	–	4	1
Conjunctivitis	1	4	11	7	9	4
Nausea/vomiting						
Grade 1–2	16	14	17	8	22	7
Grade 3–4	–	–	2	1	3	–
Leukopenia						
Grade 1–2	5	4	6	4	1	3
Grade 3–4	–	–	–	–	–	1
Thrombocytopenia						
Grade 1–2	2	2	2	1	1	1

Table 4 Objective responses

	< 65 years of age (133 patients)	≥65 years of age (82 patients)
Complete response	10 (7.5%)	4 (4.9%)
Partial response	21 (15.8%)	11 (13.4%)
Total	31 (23.3%)	15 (18.3%)
Minor response	10 (7.5%)	7 (8.5%)
Stable disease	45 (33.8%)	36 (43.9%)
Progressive disease	44 (33.1%)	21 (25.6%)
Not evaluable	3 (2.3%)	3 (3.6%)
Total	102 (76.7%)	67 (81.7%)
Objective responses	23% (95% CL 17–32)	18% (95% CL 11–29)

Only a few studies have analysed 5-FU toxicity in terms of age [14, 17]. Results from a randomized trial of 5-FU-based chemotherapy conducted by the Gastrointestinal Tumor Study Group indicate that advanced age is an independent risk factor for severe toxicity: leukopenia, diarrhoea, emesis, multiple organ system toxicity and treatment mortality were significantly more severe in the elderly group. The treatment arms were similar to those included in the present study. Since no age-dependent association was observed between side effects and chemotherapy regimen, and no pharmacokinetic differences were demonstrated, the authors suggested that a predisposition to toxicity in the elderly might be correlated with an impairment in physiological compensatory mechanisms [14]. Other studies in colorectal cancer have not found any correlation between age and toxicity [13, 15].

Obviously the results of this retrospective analysis cannot be extrapolated to all clinical trials, expecially those using other chemotherapeutic agents, alone or in combination, or to other neoplastic diseases characterized by a different natural history [16]. Clearly, elderly patients enrolled into clinical trials represent a selected population. First, approximately 40% of colorectal patients overall are not being appropriately referred for therapy, as suggested in a recent international survey of oncology specialists [3]. Furthermore, it has been suggested that the advice they receive from physician and their own desire leads elderly patients to receive significantly less comprehensive cancer therapy compared with younger patients [5]. Advanced age is not a contraindication for the use of chemotherapy, and in particular of 5-FU-based regimens, but close monitoring, supportive care, and careful patient selection are essential. However, inadequate treatment for a chemoresponsive tumour may be worse than chemotherapy toxicity. Indeed, recent reports have suggested a significant dose-response relationship for some solid tumours within the standard dosing range [8, 18], and that first-cycle dose-intensity may be particularly important. Therefore, dose reduction based on age could negatively affect outcome. Obviously, greater toxicity is acceptable when the goal of treatment is cure rather than palliation. The therapy of advanced disease is essentially not curative and therefore the main object of treatment becomes the enhancement of quality of life.

Appropriate clinical trials in the elderly are imperative. However, according to Litchman and Bayer, the elderly continue to be underrepresented in clinical trials, and the reasons include: (1) the presence of comorbidity, (2) a lack of financial, logistic and social support for participation in clinical trials, and (3) limited expectations of long-term benefits from physicians, relatives and the patients themselves [2].

References

1. Hryniuk W, Bush H (1984) The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2: 1281
2. Litchman SM, Bayer RL (1997) Gastrointestinal cancer in the elderly. In: Whitaker K (ed), Balducci L (Guest ed) Clinics in geriatric medicine. Cancer in the elderly part II. W.B. Saunders Company, Philadelphia, p 307
3. Macdonald JS on behalf the International Working Group in Colorectal Cancer (1996) A study of the treatment and management of advanced colorectal cancer: the colorectal care pathway review (abstract 563). Proc Am Soc Clin Oncol 15: 230
4. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207
5. Newcomb PA, Carbone PP (1993) Cancer treatment and age: patient perspectives. J Natl Cancer Inst 85: 1580
6. Nobile MT, Rosso R, Sertoli MR, Rubagotti A, Vidili MG, Guglielmi A, Venturini M, Canobbio L, Fassio T, Gallo L, Galligioni E, Gallotti P, Bruzzi P, Sobrero A (1992) Randomised comparison of weekly bolus 5-fluorouracil with or without leucovorin in metastatic colorectal carcinoma. Eur J Cancer 11: 1823
7. Nobile MT, Barzacchi MC, Sanguineti O, Chiara S, Gozza A, Vincenti M, Lavarello A, Cognein P, Lionetto R, Percivale PL, Bertoglio S, Murolo C, Esposito M, Vannozzi MO, Rosso R (1998) Activity of high dose 24 hour 5-fluorouracil infusion plus L-leucovorin in advanced colorectal cancer. Anticancer Res 18: 517
8. Ozols RF, Thigpen JT, Dauplat J, Colombo N, Piccart MJ, Bertelsen K, Levin L, Lund B (1993). Dose intensity. Ann Oncol 4 [Suppl.4]: 49
9. Piedbois P, Buyse M, Rustum Y, Machover D, Erlichman C, Carlson RW, Valone F, Labianca R, Doroshow JH, Petrelli N (Writing Committee) for the Advanced Colorectal Cancer Meta-analysis Project (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 10: 896
10. Piedbois P, Buyse M, Blijham G, Glimelius B, Herrmann R, Valone F, Carlson R, Machiavelli M, Delfino C, Abad A, and Petrelli N (Writing Committee) for the Advanced Colorectal Cancer Meta-analysis Project (1994) Meta-analysis of

randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. J Clin Oncol 12: 960
11. Poon MA, O'Connell MJ, Moertel GG, Wieand HS, Culliman SA, Everson LK, Krook JE, Ailliard JA, Laurie JA, Tschetter LK, Wiesenfeld M (1989) Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 7: 1407
12. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D (1993) Randomized comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. BMJ 306: 752
13. Sobrero A, Guglielmi A, Aschele C, Tixi L, Bolli E, Mori A, Rosso R, Lionetto R, Bruzzi P (1994) Adjuvant chemotherapy of elderly patients with colorectal cancer. Proceedings Second International Conference on Geriatric Oncology – Cancer in the Elderly – Genoa, 19–21 September Tormena Industril Coroficle, Genoa, p. 111
14. Stein BN, Petrelli NJ, Douglass HO, Driscoll DL, Arcangeli G, Meropol NJ (1995) Age and Sex are independent predictors of 5-fluorouracil toxicity: analyses of a large scale phase II trial. Cancer 75: 11
15. Steinberg J, Erlichman C, Gadalla T, Fine S, Wong A (1992) Prognostic factors in patients with metastatic colorectal cancer receiving 5-fluorouracil and folinic acid. Eur J Cancer 28A: 1817
16. Tirelli U, Zagonel V, Serraino, Thomas J, Hoerni B, Tangury A, Ruhl U, Bey P, Tubiana N, Breed WPM, Roozendaal KJ, Hagenbeek A, Hupperets PS, Somers R (1998) Non-Hodgkin lymphoma in 137 patients aged 70 years or older: a retrospective European Organization for Research and Treatment of Cancer Lymphoma Group study, J Clin Oncol 6: 1708
17. Vokes EE, Ratain MJ, Mick R, McEvilly JM, Haraf D, Kozloff M, Hamasaki V, Weichselbaum RR, Panje WR, Wenig B, Berezin F (1993) Cisplatin, fluorouracil, and leucovorin augmentated by interferon alfa-2b in head and neck cancer: a clinical and pharmacologic analysis. J Clin Oncol 11: 360
18. Wood WC, Budman DR, Korzun AH, Cooper MR, Younger J, Hart RD, Moore A, Ellerton JA, Norton L, Ferree CR, Ballow AC, Frei E III, Henderson C (1994) Dose and dose-intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 330: 1253