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Cancer chemotherapy in the elderly: a series of 51 patients aged >70 years*

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Summary. A total of 2,238 new cancer patients were treated in our institution in 1988; among the 423 (18.9%) who were >70 years old, 51 underwent chemotherapy. The median age was 75.8 years, and the Karnofsky performance status (KPS) was $\geq 70\%$ for 40 patients. Malignancies were hematopoietic in 24 cases (47%) and digestive in 15 patients (29%), and 12 subjects (24%) had other types of cancers. The first chemotherapy course was given at the full dose to 23/51 (45.1%) patients. The drug dose was reduced for 28/51 (54.9%) patients, due in 25 cases to the subjects being >70 years old. Neither age, KPS, pretreatment assessment, nor cancer extent was correlated with the modifications made to the first cycle. An overall toxicity of grade 3 + 4 (WHO grading scale) was noted in 10 subjects (19.6%). Although these elderly patients were probably selected, analysis of their charts did not evidence an increase in chemotherapy toxicity, regardless of the dose they received.

Introduction

The population of the elderly is growing rapidly. The incidence of cancer is increasing with age [16], and half of all cancers presently occur in patients aged >70 years [25]. Data from Samet et al. [19] show that the proportion of cancer patients receiving curative therapy declines with age. However, among the modes of treatment used, chemotherapy is rarely given, mainly because of the notion of an increased incidence and severity of side effects in the elderly. In fact, many papers have dealt with this subject [2, 3, 10]; chronological age does not appear to be a predictor of (poor) tolerance or (lack of) response in the elderly [8, 9]. The purpose of the present study was to analyse retrospectively the charts of patients aged >70 years who were treated with chemotherapy in our institution in 1988 and to determine whether the usual dose reductions are justified by an actual increased risk of toxicity.

Patients and methods

Patients. Elderly patients were defined as being >70 years of age, and patients treated during 1988 were studied so as ensure a sufficient to follow-up period. Between January 1st and December 31st, 1988, 2,288 new cancer patients were treated in our institution. Of these subjects, 423 (18.9%) were aged >70 years, and only 59 (14.1%) received chemotherapy. During the same period, the other 1,865 patients were aged <70 years, and 577 of them (30.9%) underwent chemotherapy. Of the 59 elderly patients who were treated by chemotherapy, 51 were evaluable for this retrospective study; we deliberately excluded 2 subjects who were given only intrathecal chemotherapy, 5 who were treated with a single drug (cyclophosphamide tablets) for several months, and a 78-year-old man who died of peritonitis within 2 weeks of the initiation of chemotherapy and was thus nonevaluable for efficacy or toxicity.

All patients exhibited histologically proven cancer, and their characteristics are summarized in Table 1. The disease was locoregional in 25 cases, disseminated in 14 subjects and locoregional and disseminated in 12 patients. In all, 12 subjects displayed pathologic antecedents, including hypertension ($n = 4$), angina pectoris ($n = 2$), cardiac failure ($n = 3$), diabetes mellitus ($n = 2$) and chronic respiratory disease ($n = 1$). Three patients had also previously been treated for and cured of another cancer (cervical, gastric, prostatic). Pretreatment assessment was normal in 41 subjects and abnormal in 10. Abnormalities involved electrocardiograms (ECGs, $n = 5$), hematologic counts ($n = 3$), liver function tests ($n = 6$) and serum creatinine levels ($n = 10$). All abnormal liver tests, one abnormal ECG and one abnormal hematologic count were attributable to the extent of disease.

Treatment. The indication for chemotherapy on the present treatment schedule was palliative in 30 cases and curative in 21; in the latter, chemotherapy alone was given to 4 patients; adjuvant chemotherapy, to 2 (after surgery and prior to radiotherapy for gastric carcinoma); and neoadjuvant chemotherapy, to 15 (before radiotherapy in 10 cases, prior to radiotherapy + chemotherapy in 4 subjects and before surgery and radiotherapy in 1 case).

The chemotherapy protocols used were considered to be standard treatment in our institution, i.e. there was no specific regimen for these patients. Many agents and combinations were used, and these are listed in Table 2. Most protocols for malignant non-Hodgkin's lymphoma con-

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Table 1. Patients' characteristics

Characteristics	Number of patients	
Sex:		
M	24	(47%)
F	27	(53%)
Median age (range)	75.8	(70–90) years
Age frequency:		
70–74 years	23	(45.1%)
75–79 years	22	(43.1%)
80–91 years	6	(11.8%)
Karnofsky performance status:		
≥70%	40	(78.4%)
<70%	11	(21.6%)
Cancers:		
Hematopoietic diseases	24	(47%)
Malignant non-Hodgkin's lymphomas	19	
Hodgkin's disease	2	
Leukemias	3	
Digestive diseases	15	(29%)
Oesophageal	2	
Gastric	7	
Colon and rectum	3	
Anal canal	3	
Other	12	(24%)
Breast carcinoma	4	
Sarcomas	3	
Ovarian carcinoma	2	
Head and neck cancer	1	
Oat-cell lung cancer	1	
Carcinoma of unknown primary origin	1	

sisted of doxorubicin (35 mg/m^2 on days 1 and 15), cyclophosphamide (400 mg/m^2 on days 1, 8 and 15), vincristine (0.7 mg/m^2 on days 1, 8 and 15) and prednisone (40 mg/m^2 daily for 15 days), with therapy being resumed on day 28. Oesophageal and anal canal cancers were treated with a combination of cisplatin (100 mg/m^2 on day 1) and 5-fluorouracil (5-FU; 1,000 mg/m^2 on days 2–6) every 3 weeks; gastric cancers were treated with a combination of 5-FU (600 mg/m^2 on day 1), doxorubicin (30 mg/m^2 on day 1) and cisplatin (80 mg/m^2 on day 1) every 4 weeks or with mitomycin C (10 mg/m^2 on day 1) and 5-FU (1,000 mg/m^2 on days 1–5) every 4 weeks. The mean number of chemotherapy courses given (regardless of the disease treated or the protocol used) was 2.5 (range, 1–7), and 45/51 patients (86.4%) received 1–3 courses.

Monitoring. All patients underwent a complete physical examination, blood cell counts, liver function tests, ECG and chest radiography, before treatment. Other investigations were done as needed (e.g. abdominal ultrasound, computed tomographic (CT) scan or endoscopy). Clinical and biological examinations were performed only prior to each treatment course (which probably led us to underestimate toxicities). Toxic effects were documented as representing acute or subacute toxicity and were evaluated prior to each chemotherapy cycle; we used the five-grade system recommended by the WHO for reporting the toxicity of cancer treatment [15]. In our institution, overall toxicity is calculated as the sum of the worst WHO-scale toxicities encountered in one subject and then as the sum of the worst toxicities encountered in all patients. Standard WHO criteria were also used to evaluate efficacy [15]; a complete response (CR) was defined as the disappearance of all perceptible tumors and a partial response (PR) was defined as a reduction of at least 50% in the total tumor mass in the absence of any evidence of progressive disease elsewhere following two cycles of chemotherapy. No change (NC) was assumed when neither a 50% tumoral decrease nor a 25% increase in measurable lesion size could be established. Progressive disease (PD) represented an increase of ≥25% in the size of one or more evaluable lesions or the appearance of new lesions.

Statistical methods. Survival was calculated from the start of chemotherapy. Comparisons were made using the Mantel-Haenszel chi-square statistical test, which is more robust when strata contain small frequencies.

Results

Initial chemotherapy doses

The first course was given at the full dose to 23/51 patients, and the drug dose was reduced for 28/51 subjects. In only three cases was this due to pretreatment abnormalities: one case of creatinemia (145 μg/ml), one pericardial effusion and one case of leucothrombocytopenia. For 25/28 patients, the decision to reduce the drug dose was based only on age (even if no concomitant disease was noted). When age frequency is considered, an age of 70–74, 75–79 or >80 years had no influence on the effect of a full vs a reduced dose of chemotherapy on our sub-

Table 2. Chemotherapy protocols

Site	Number of cases	Drugs used	Number of patients receiving the drug
Malignant non-Hodgkin's lymphoma	19	Anthracyclines	14
		Cyclophosphamide	18
		Vincristine	19
		Steroids	19
Hodgkin's disease	2	Epirubicin, bleomycin, vinblastine, steroids	2
Leukemias	2	Chlorambucil	2
Gastric	7	5-FU, doxorubicin, cisplatin	6
		5-FU, mitomycin C	1
Oesophageal	2	5-FU, cisplatin	2
Anal canal	3	5-FU, cisplatin	3
Colon and rectum	3	Folinic acid, 5-FU	3
Other	12	Miscellaneous protocols	12

jects. Similarly, there was no correlation between a Karnofsky performance status of 60%, 70% or 80% and a dose reduction for the first course of treatment. Moreover, whether the patients were treated with a curative or a palliative intent, they received the same ratio of a full or reduced dose of chemotherapy. Finally, protocol alterations were well balanced between the different groups of cancer patients.

During the first course, a drug dose reduction "for age only" involved the treatment of 14 malignant non-Hodgkin's lymphomas (MNHL), 5 gastrointestinal tract cancers, 2 sarcomas and 4 miscellaneous cancers. Concerning the three drugs we eventually used and whose use in the elderly is often debated, i.e. anthracyclines, cisplatin and 5-FU, the following may be noted: doxorubicin (at 35 mg/m^2) and epirubicin (at 60 mg/m^2) were systematically discontinued in the treatment of MNHL (whether aggressive or not), whereas doxorubicin (at 30 mg/m^2) was always delivered at the full dose to patients with gastric cancers. Cisplatin, which was mainly used to treat digestive cancers, was delivered without modification when the protocol dose indicated 80 mg/m^2, but the dose of this drug was reduced by 25% in half of the patients when the scheduled dose was 100 mg/m^2. Treatment with 5-FU required no dose modifications for gastric and colorectal cancer patients when the protocols called for bolus i.v. injections at doses ranging from 400 to 600 mg/m^2 daily; when 5-FU was scheduled to be delivered at 1,000 mg/m^2 daily by continuous infusion (oesophageal and anal canal cancers), the dose was systematically reduced by 25%.

Toxicity

Toxicity could be evaluated according to WHO criteria in all 51 patients and is shown in Table 3. No iatrogenic death occurred, and one treatment had to be stopped due to severe nausea, vomiting and diarrhoea that required therapy for 10 days. Among the 11 elderly patients who experienced a WHO toxicity of grade 3 or 4 (19.6%) 6 had received a full-dose cycle and 4 had been given a reduced-dose cycle. Digestive toxicity (grade 2 or 3) occurred in 12 subjects (23.5%) and mainly involved gastrointestinal tract cancer that was being treated with 5-FU and/or cisplatin and/or doxorubicin. Hematologic toxicity (grades 2, 3 or 4) occurred in 8 patients (15.5%) and was mainly encountered in those exhibiting hematologic cancers (MNHL or leukemia). Nevertheless, regardless of whether a full or a reduced dose of chemotherapy was delivered, no statistically significant correlation ($P = 0.48$) was found with the overall toxicity noted.

Efficacy

Efficacy could be evaluated in 48/51 patients; 2 subjects underwent adjuvant chemotherapy (for gastric cancer) and one patient died intercurrently of Mendelson's syndrome after completing two courses of treatment. Difficulties in analysis arose due to the heterogeneity of cancer types and of chemotherapy protocols. PRs and CRs were shown by patients with MNHL (9/19, 47%), Hodgkin's disease (2/2), and gastrointestinal tract cancers (6/9). Among the latter, 2/4 gastric cancers responded to chemotherapy (on a 5-FU/doxorubicin/cisplatin protocol), and 4/5 oesophageal and anal canal cancers responded to a cisplatin/5-FU combination. Again, no statistical correlation was found with respect to the chemotherapy doses given.

Table 3. Toxicity of chemotherapy in elderly patients

Toxicity	Number of patients showing toxic effects of WHO grade				
	0	1	2	3	4
Nausea and vomiting	31	11	7	2	0
Diarrhoea	36	8	6	1	0
Oral mucositis	40	7	1	3	0
Infection	48	3	0	0	0
Haemorrhage	50	0	1	0	0
Leucocytes	20	27	2	1	1
Platelets	43	6	1	0	1
Hemoglobin	22	25	2	2	0
Creatinine	50	0	1	0	0
Cardiac function	51	0	0	0	0
Peripheral neurotoxicity	51	0	0	0	0

Survival

Overall survival was evaluated over all chemotherapy protocols and all treatment combinations. For example, the non-corrected median survival of all patients with MNHL was 17.6 months (range, 2–25$^+$ months), with 9/24 subjects showing no evidence of disease. In subjects exhibiting gastrointestinal tract cancers, the median survival was 11.6 months (range, 2–25$^+$ months), with 5/15 patients showing no evidence of disease (3 were treated for anal canal cancer and 2, for gastric cancer).

Discussion

Cancer in the elderly is a common problem because half of the new malignancies that develop occur in this group and because treatment remains poorly defined for them. Patients aged >70 years are usually excluded from clinical trials [11]. As compared with younger subjects, they often appear to be undertreated because of their increased risk of developing chemotherapeutic side effects [9, 24]; this fear became apparent in our retrospective study, since 25/51 patients received arbitrarily decreased doses based solely on their age being >70 years. This problem is currently a matter of debate among medical oncologists [13, 20]: in practice, the decreased chemotherapy doses that are delivered may be related to the extent of the disease (metastatic or not) or to the specific drugs used; 5-FU given by continuous infusion or treatment with cisplatin (with associated saline hydration) often lead to reduced doses in elderly patients, even in the absence of pretreatment abnormalities [24].

In the elderly, the patterns of chemotherapy-induced toxicity appear to be similar to those observed in younger patients [3]; in fact, as noted in the treatment of anal canal cancers with neoadjuvant chemotherapy [5], elderly subjects display the same kinds of toxic effects as do younger patients. Moreover, there was no increase in the frequency or severity of toxicity during the present study, whether or not the doses given were systematically reduced; however, due to the heterogeneity of the tumor types and of the number of different protocols, the statistical power of the tests we used may have been diminished and the possibility of false-negative results cannot be excluded.

Nevertheless, a good tolerance of chemotherapy has also been reported for patients aged >70 years who had been treated for lung, colon and breast cancers in a retrospective study of the Eastern Cooperative Oncology Group (ECOG) [2]. In another ECOG trial on poor-prognosis elderly MNHL patients [17], a similar frequency and severity of toxicity was encountered when a full or reduced dose of chemotherapy was delivered. Recently, Sonneveld and Michiels [21] reported on a prospective study of elderly MNHL patients who received full doses of chemotherapy without developing serious toxicity. In contrast, the EORTC Lymphoma Group observed significantly more severe and lethal side effects in elderly subjects who received aggressive treatment for MNHL [22]. In our institution, Hoerni et al. [12] and Eghbali et al. [7] retrospectively reviewed the data on elderly patients who had been treated for MNHL [12] and Hodgkin's disease [7]; subjects had received chemotherapy according to their clinical stage and histological type or grade (sometimes combined with other treatment), and all of the lethal side effects in these series occurred when elderly patients were treated with aggressive and full-dose protocols. These apparently conflicting results may partly be explained by (a) patient selection with respect to performance status and/or disease extent (this was probably the case in our study, as 40 subjects had a KPS of $\geq 70\%$) [14] and (b) evaluation of physiological functions in the elderly, especially renal function, which decreases with age and is better estimated by creatinine clearance than by creatininemia [1, 18]. For example, Gelman and Taylor [10] treated advanced breast cancer patients aged 65–90 years with a cyclophosphamide/methotrexate/5-FU (CMF) regimen; the initial doses were adapted to creatinine clearance, with the result being that no association between toxicity and age could be demonstrated for this modified protocol.

In the present study, the question as to whether the response to chemotherapy was reduced with age remains unanswered; this aspect was difficult to analyse due to the heterogeneity of cancer types, disease extent and chemotherapy protocols. Nevertheless, among the patients for whom chemotherapy was part of a curative treatment plan, the response rates observed were comparable with those noted for younger subjects in terms of both CRs and PRs, regardless of the chemotherapy dose levels. Similar rates of response among patients undergoing palliative treatment have also been observed in elderly subjects with disseminated MNHL [4]; no significant difference in CRs was found between patients who received combination chemotherapy comprising cyclophosphamide, vincristine and prednisone, subjects who were given the same regimen plus anthracyclines, and individuals who received a high-dose regimen containing anthracyclines. In contrast, Dixon et al. [6] reviewed elderly patients with advanced MNHL who had been treated in Southwest Oncology Group (SWOG) trials and noted that the "CR rates declined progressively with advancing age". As an initial dose reduction of 50% had been planned for subjects aged >65 years, the response rates may have been underestimated, since neither Vose et al. [23] nor Sonneveld and Michiels [21] found any significant difference in CR/PR rates with age in patients who underwent full-dose chemotherapy.

The survival benefit for elderly patients receiving chemotherapy is also difficult to analyse. The overall non-corrected median survival of our MNHL patients was 17.6 months, including those who were treated with a curative intent (whether or not they received full-dose chemotherapy) and those who underwent palliative treatment for stage III or IV tumors. As compared with that observed in younger patients, this survival rate appears disappointing. However, it also takes into account all causes of death that were not obviously related to the cancer or its treatment. These results are consistent with those obtained by Vose et al. [23], who found that mortality due to lymphoma or to its treatment side effects were similar for patients both under and over 60 years of age and that the shorter overall survival of the elderly was attributable to non-neoplastic causes. Moreover, Brice et al. [4] noted a similar survival value for elderly MNHL patients who were treated with a classic chemotherapy regimen without anthracyclines as compared with a high-dose intensive regimen. If one then considers the survival of subjects exhibiting digestive cancer, good results were obtained for gastric and anal canal cancers (11.6 months); all 3 anal canal cancers and 3/7 gastric cancers in this series were treated with a curative intent. Begg and Carbone [2] found similar survival curves for both elderly and non-elderly patients who were treated for lung, colon and breast cancers, independent of the chemotherapy given.

The conclusions drawn from this retrospective study are the following: (1) elderly patients should undergo a thorough work-up with regard to their general and visceral status, the extent of their disease and the possibility of treatment; (2) chronological age alone is not sufficient to limit or contraindicate chemotherapy, and this may explain the lack of differences encountered for the same chemotherapy regimen given at full vs reduced doses; (3) for an elderly patient showing a good probability of cure, the therapeutical approach considered should be the same as that for a younger person presenting with an equivalent disease; and (4) incurable elderly subjects may be considered to be eligible for chemotherapy if they exhibit a good general status and a treatment-sensitive tumor, as the achievement of a PR or even of stable disease may provide them with at least an acceptable quality of life, if not with prolonged survival.

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