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Non-Hodgkin's Lymphomas in the Elderly: Prospective Studies with Specifically Devised Chemotherapy Regimens in 66 Patients

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Abstract—*The results of 2 consecutive and prospective trials with specifically devised chemotherapy regimens in elderly patients (pts) with non-Hodgkin's lymphoma (NHL) are reported. Between August 1979 and September 1984, 66 pts aged 70 or older (median 75 years) with NHL entered 2 consecutive trials, the former with single agent teniposide 100 mg/m² i.v. weekly (41 pts), the latter with etoposide and prednimustine (E + P), 100 mg/m p.o. for 5 days every 21 days (25 pts). Forty-five pts were previously untreated, 21 previously treated. Forty-seven pts were of the intermediate and high grade groups according to the Working Formulation; 19 pts were of the low grade; 57 pts were stages III and IV, 9 pts were stages I and II. The median performance status was 70 (range 30–100). The objective response rate in the 66 evaluable pts is 53% with 38% CR; the 3-year overall, disease-free and CR survivals are 21, 12 and 40% respectively. The objective response rate in the 45 previously untreated pts is 58% with 42% CR; the 3-year overall, disease-free and CR survivals are 24, 16 and 58% respectively. The overall toxicity was mild. Severe toxicity (grade III and IV according to WHO criteria) was observed only in 16/498 courses (3.2%), with 1 toxic death (grade IV leucopenia). We experienced the usefulness of a properly orientated clinical approach to elderly pts with NHL. We suggest that a combination regimen like E + P, suitable for oral administration, may be safely employed in a large fraction of pts with NHL.*

INTRODUCTION

In Western countries, people aged 65 years or more account for 10–14% and their number is increasing [1]. Fifty per cent of cancers occur in the elderly [2], who actually represent only a small fraction of patients eligible for clinical trials [3]. The low recruitment of these patients, even in potentially curable malignancies as non-Hodgkin's lymphoma (NHL), is often due to the toxicity of currently available regimens. Elderly patients constitute a relevant proportion of all patients with NHL, varying from 17.7 to 38.5% in a wide series of reports [4–7]. Nevertheless, clinicopathologic studies in NHL are few and scattered, in particular, there are no reports of prospective treatments on these patients. Recently, Armitage and Potter have retrospectively evaluated the outcome of patients 70 years of age or older with diffuse histocytic lymphoma and predominantly [75%] advanced stage disease with the CHOP regimen (cyclophosphamide, adriamycin, vincristine and prednisone) at full doses [8]. Although the complete remission (CR) rate observed was not significantly different from that of a younger group of patients with diffuse histocytic lymphoma treated concurrently with CHOP, 30% treatment-related deaths occurred, the major factor being sepsis. On the other hand, Miller and Jones reported a series of 11 patients older than 65 years with clinically localized NHL of unfavourable histology treated with CHOP at initial doses reduced to 50% of the calculated full dosage [9]. Toxicity reported was generally mild and 10 of the 11 patients remain continuously free of disease at the time of the report. However, 7 out of 11 patients received only 2–4 courses of the initial

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CHOP because of prolonged myelosuppression and then were treated with radiation therapy. It is conceivable from this experience that patients who are likely to need more prolonged treatment, i.e. those with advanced stage unfavourable NHL, may not be able to receive CHOP, even at reduced doses, without significant toxicity.

Since 1979, prospective studies in the treatment of NHL of the elderly have been on-going at our institution. The aim of these studies is to prospectively evaluate specifically devised chemotherapy regimens for elderly patients (arbitrarily defined as 70 years of age or older) with NHL.

In this paper we have chosen to report the cumulative data obtained from 2 different but consecutive trials because of the similarity of treatments employed (epipodophyllotoxins ± prednimustine) and the homogeneity of the study populations.

PATIENTS AND METHODS

In August 1979, a phase II trial of teniposide (VM-26) in patients with NHL was activated at our institution. Preliminary results in 22 elderly patients (70 years or more) of this group, as of October 1982, have been previously reported [10]. Since the start of ths trial, all consecutive previously untreated patients 70 years of age or more with stages III and IV, irrespective of histologic type, performance status (PS), concomitant disease, or prior treatment seen at our institution, were admitted to the trial. A modified Rappaport classification [11] was applied to all patients. Nodular histocytic, diffuse histocytic, lymphoblastic and Burkitt's were considered 'unfavourable' NHL subtypes, whereas the remaining subtypes were considered to be 'favourable'. All the histological diagnoses were reviewed by the same pathologist (A.C.) and on that occasion they were also re-classified according to the Working Formulation [12].

Prior to the initiation of teniposide therapy, previously untreated patients were staged with procedures selected for each patient, according to PS, age, clinical presentation and histology. Clinical examination, routine blood analysis and chest X-ray were performed in all patients, whereas bone marrow biopsy and/or aspirate, abdominal computerized tomography and/or lymphangiogram, laparoscopy with spleen and liver biopsies were performed in selected patients. Previously treated patients were submitted to those examinations thought to be useful for tumour extent evaluation. All patients were clinically classified according to Ann Arbor staging system [13]. Teniposide was administered by i.v. infusion over a minimum of 30 min at 100 mg/m^2 weekly for at least 3 weeks to patients with 'unfavourable' subtypes and for at least 6–9 weeks to patients with 'favourable' subtypes, prior to evaluation for response. For patients achieving CR, 4 additional doses were given and then treatment was discontinued. Pathologic confirmation of clinical CR was sought only in a few selected patients, depending on site(s) of previous disease, PS and age. No consolidation radiotherapy was given. The teniposide dose was reduced by 50% for white blood counts between 2500–4000/cu.mm and/or for platelet count between 50–100,000/cu.mm. In the presence of lower counts, weekly delays in re-treating were adopted until recovery.

In April 1983, a subsequent phase II study with etoposide and prednimustine (E + P) was activated. Criteria for patient selection were: all consecutive and previously untreated patients 70 years of age or older with stages I, II, III and IV unfavourable histology (intermediate and high-grade category of Working Formulation), and stage III and IV favourable histology (low-grade category of Working Formulation) with symptomatic disease. The Working Formulation criteria were prospectively applied to all patients, in addition to a modified Rappaport classification [11]. Staging procedures were those employed in the teniposide trial. Etoposide and prednimustine were both given orally at doses of 100 mg/m^2 for 5 days every 3 weeks for at least 2 cycles prior to the evaluation of response. Etoposide capsules or etoposide vials for parenteral administration were taken orally. Responding patients with stage I and II were treated for 9 cycles, whereas these with stage III and IV were treated for 12 cycles. In cases of CR, 2 cycles of consolidation therapy were given and then treatment was discontinued. No consolidation radiotherapy was given. In cases of bone marrow toxicity dosage reduction of E + P was made as in the teniposide trial.

Assessment of toxicity and evaluation of response were performed in both trials according to WHO criteria [14]. Survival was calculated by means of the Life Table method [15].

RESULTS

Between August and September 1984, 66 consecutive elderly (70 years or more) patients with NHL entered the studies, 41 in the teniposide trial and 25 in the subsequent E + P trial.

Patients' characteristics are summarized in Table 1. Forty-five patients were previously untreated, whereas 21 were previously treated, with a median number of 2 regimens and 7 drugs, respectively. Forty-seven patients had high or intermediate grades according to Working Formulation, 19 patients had low grades, 15 of whom had symptomatic disease. Fifty-seven patients were stages III and IV, 9 were stages I and II; 42 of the former group were in the low-grade category. Median Karnofsky PS was 70 (range 30–100) in both trials.

Table I

Patient characteristics	Teniposide	E + P	Overall
No. of patients	41	25	66
Sex (M/F)	25/16	17/8	42/24
Median age (range)	75 (70–85)	76 (70–86)	75 (70–86)
Median PS (range)	70 (30–100)	70 (30–100)	70 (30–100)
No. of patients previously untreated	27	18	45
No. of patients previously treated	14	7	21
No. of patients with:			
stages I & II	3	6	9
stages III & IV	39	19	57
low grade WF	13	6	19
intermediate WF	13	8	21
high grade WF	15	11	26

WF = Working Formulation.

Table 2. *Response and survival*

No. of evaluable patients		Response CR (%)	PR (%)	3-year survival Overall (%)	Disease-free (%)	CRs (%)
No. of total patients:	66	38	15	21	12	40
No. of patients on teniposide trial	41	32	20			
No. of patients on E + P trial	25	48	8			
No. of previously untreated patients	45	42	16	24	16	58
No. of patients on teniposide trial	27	44	15			
No. of patients on E + P trial	18	39	17			

Five patients, 2 on the teniposide trial and 3 on the E + P trial, all previously untreated, died prior to the completion of the scheduled 2 cycles of chemotherapy. Only 1 of these 5 deaths was treatment-related. All these early deaths were included in the calculation of the response rate and were considered failures.

Response and survival are reported in Table 2. The objective response rate in the 66 evaluable patients is 53% with 38% CR. The 3-year overall, disease-free and CR survivals are 21, 12 and 40%, respectively.

The objective response rate in the 45 previously untreated patients is 58% with 42% CR. The 3-year overall, disease-free and CRs survivals are 24, 16 and 58%, respectively.

There are no significant differences in response and survival as far as stage, histology, prior treatment and PS are concerned.

Among the high and intermediate grade categories of Working Formulation, diffuse histocytic or corresponding group of Working Formulation constitutes 32% of cases. The overall response in the latter 15 patients was 75% with 53% CR; the 3-year overall, disease-free and CR survivals are 47, 27 and 62.5%, respectively.

Table 3. *Toxic episodes in* 498 *evaluable courses*

Type of toxicity	Grade of toxicity G_1	G_2	G_3	G_4
Nausea and vomiting	9	6	—	—
Alopecia	—	9	8	—
Leukopenia	37	38	5	1*
Anaemia	3	4	1	—
Trombocytopenia	5	2	1	—

*Resulting in death.

Toxicity is reported in Table 3. Severe toxicity (WHO grades III and IV) was observed oly in 16/498 (3.2%) courses; however, 1 toxic episode (grade IV leucopenia) resulted in death in a previously untreated patient of the teniposide trial.

Up to October 1984, 43 patients have died and 23 patients are still alive.

DISCUSSION

There appears to have been very little published work dealing with cancer chemotherapy in the elderly. In a retrospective analysis of data from 8 different neoplastic diseases, but not including lymphoma and leukaemia, ECOG investigators did not find any increase in toxicity in elderly patients, defined as 70 years or older, receiving chemotherapy [16]. However, there might have been a favourable patient selection, as suggested by the authors, and the median age of this patient population was not reported [16]. On the other hand, a randomized study conducted by the same group, comparing full vs. attenuated doses of the same regimen (daunorubicin, cytosine arabinoside and 6-thioguanine) in acute non-lymphocytic leukaemia in the elderly demonstrated that with the full dose regimen the risk for early death was more than twice that of the attenuated regimen, without differences in remission rates [17]. A similar high treatment-related death rate has been suggested for elderly patients with Hodgkin's disease treated with chemotherapy. In a group of 19 patients older than 70 years, 4 patients died for causes related to the treatment (3 patients had been treated with MOPP of CVPP, and 1 patient with single agent procarbazine) [18].

The use of chemotherapy in the elderly is associated with many problems, i.e. there is a diminished bone marrow capacity of regeneration and a higher possibility of cardiac and lung toxicities, the distribution of the drugs may be modified, the renal and hepatic excretion may be altered [19]. In addition, concomitant chronic illness and subsequent use of multiple drugs enhance the risk of interactions and adverse drug reactions. For all these reasons, most clinicians seem to be reluctant to treat elderly patients affected by malignancies with conventional chemotherapy regimens.

Since the attempt to obtain a CR with standard regimens in the elderly with NHL increases the risk of haematological toxicity and death from the complications of treatment [8], in 1979 we wondered whether a less intensive therapy with less toxic drugs would have given comparable results, possibly with improvement of overall survival. The first trial evaluated teniposide at a weekly i.v. infusion schedule in 41 consecutive elderly patients with NHL. Teniposide was chosen because of the high activity and very low toxicity shown by EORTC [20] and Chiuten *et al.* [21] studies in patients with NHL. However, some patients had problems in complying with the i.v. schedule of teniposide. In April 1983, we decided to use the other podophyllotoxin etoposide, suitable for oral administration, instead of teniposide. Etoposide had shown approximately the same activity of teniposide in NHL [22]. After oral administration, the availability of etoposide appears to be variable, the absorption from ampules being slightly more than 50% of a given dose [23]. Moreover, we designed a new regimen, adding to etoposide a new drug, prednimustine, a prednisolone ester of chlorambucil. Prednimustine had shown marked activity against NHL in several European trials, the overall response rate in 128 patients being 77% [24]. Moreover, toxicity, mainly haematologic, was minimal. A recent study has shown that although prednimustine was well absorbed, the ester was subjected to extensive presystemic metabolism and was not present in the systemic circulation after oral administration [25]. The efficacy reported following oral administration of prednimustine is most likely due to chlorambucil and/or prednisolone or metabolites of the compounds [25].

The vast majority of elderly patients with NHL present with advanced disease and diffuse subtype [4]. In our series, 86% of the patients had stage III or IV and 72% were in the high or intermediate grade of the Working Formulation. The present results demonstrate an overall mild toxicity (only one toxic death) with an appreciable response rate (overall 53% with 38% CR). The responses obtained in the 15 patients with diffuse histocytic subtype (53% CR) are noteworthy and compare favourably with those obtained with CHOP by Armitage and Potter in elderly patients with diffuse histocytic subtype (45% CR) at the expense of considerable toxicity (30% treatment-related deaths) [8] and with those obtained with the podophyllotoxin etoposide alone or in association with doxorubicin by Jacob *et al.* [26] in younger patients with large cell lymphoma (40 and 56% CR respectively) with mild toxicity. Furthermore, in the latter report, the 3-year overall survival in previously untreated patients of etoposide and etoposide + doxorubicin groups ranges between 30 and 40% (see Fig. 2 of Reference [26]) and is higher than the 24% observed in our 45 previously untreated patients, whereas the 3-year survival for patients achieving CR is approx. 70% (see Fig. 1 of the same Reference), higher than the 58% observed in our CRs. In addition, the overall 3-year survival observed in our previously untreated patients who achieved a CR (58%) approaches that of the entire population at age 75 in Italy (60%) [27].

In conclusion, we would like to stress that during the past 6 years of prospective management of elderly patients with NHL, we experienced the usefulness of a properly orientated clinical approach to these patients. Psychology, lifestyle and individual attitudes must be specifically taken into consideration when evaluating results in these patients.

In fact, it is possible that a number of elderly patients with NHL are lost to useful treatments because of a too aggressive approach. With these concepts in mind, the results obtained in our prospective trials would recommend an active, careful, moderately aggressive treatment of elderly patients with NHL. We suggest that a combination chemotherapy regimen like etoposide and prednimustine, suitable for oral administration, may be safely employed in a large fraction of elderly patients, particularly those with a poor general condition or advanced age (> 80 years). On the other hand, it is certain that more aggressive treatments than those employed in the present study could be tolerated by some elderly patients with possible improvement in CR rate and survival. Futher studies are needed to identify such elderly patients.

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