British Journal of Cancer (1996) 73, 794-797

Experience with poorly myelosuppressive chemotherapy schedules for advanced myeloma

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Summary In a multicentre study, 83 patients with advanced and previously uniformly treated multiple myeloma (MM) were randomised between cyclophosphamide (600 mg m^{-2}) and epirubicin (70 mg m^{-2}), administered every 3 weeks for three courses and both associated with prednisone and interferon-α2b. Both regimens were administered on an outpatient basis and had low haematological toxicity. Clinical results were similar. Overall response rate (43%) and median response and survival (5.9 and 14.1 months respectively) compare well with those obtained with more aggressive chemotherapy schedules.

Keywords: advanced myeloma; outpatient therapy; randomisation; epirubicin; cyclophosphamide

Treatment of advanced multiple myeloma (MM) usually employs combination chemotherapy (Buzaid and Durie, 1988). We used either cyclophosphamide (CTX) or epirubicin (EPI), both associated with recombinant interferon (IFN) and prednisone (P), as third-line therapy, with the expectancy that haematological toxicity would be low and the therapy feasible on an outpatient basis. All patients came from Protocol MM87 (Riccardi *et al.*, 1994), where they were treated, as first-line therapy, either with melphalan and prednisone (MPH-P) or peptichemio (PTC), vincristine (VCR) and P. As second-line therapy, patients resistant to or relapsed following one combination were crossed to the other combination.

The choice of salvage CTX came from the fact that MPH-resistant MM patients may respond to this drug (Bergsagel *et al.*, 1972; Lenhard *et al.*, 1984). The use of EPI was justified by the response of advanced patients to the several combination chemotherapies including anthracycline (Alberts *et al.*, 1976; Finnish Leukaemia Group, 1990).

Materials and methods

Between January 1989 and December 1993, 83 consecutive patients (Table I) entered a third-line, prospective, multicentre, randomised protocol (Protocol MM87/01) for advanced MM. Patients were primarily resistant to or relapsed following a response to first- and second-line therapies of Protocol MM87 (i.e. to MPH-P and PTC-VCR-P) (Riccardi *et al.*, 1994).

Randomisation was between EPI (70 mg m^{-2}) and CTX (600 mg m^{-2}) given by i.v. infusion on day 1 every 3 weeks for 3 courses. Both cytostatics were combined with P (2 mg kg^{-1} day^{-1}, days 1-4 and 11-15) and IFN-α2b (3 MU three times a week).

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Received 7 June 1995; revised 5 October 1995; accepted 31 October 1995

Response, maintenance therapy and relapse

Response was evaluated at the end of induction therapy, according to slightly modified clinical criteria (Riccardi *et al.*, 1994) adopted by the SECSG (Cohen *et al.*, 1979).

Responsive patients continued therapy until maximum reduction in monoclonal component (MC) (i.e. the plateau phase) was reached and maintained for 6 months, with stable clinical, haematological and radiological conditions. Then, they continued only on IFN-α2b (3 MU three times a week) as a maintenance therapy.

Relapse was defined as a >50% increase in the plateau level of MC and/or an increase in the size and/or number of skeletal lytic lesions.

Follow-up and statistical evaluation

The guidelines for following up MM are similar to those detailed elsewhere (Riccardi *et al.*, 1994). To define the drug toxicity blood counts were performed twice in the interval between courses.

The statistical evaluation of the differences in response rate and duration of response (from the end of successful induction therapy until relapse) and of survival (from randomisation to death) are described elsewhere (Riccardi *et al.*, 1994).

Results

In both EPI-P-IFN and CTX-P-IFN arms, patients were similar for the main clinical characteristics (Table I), and more of them had received MPH-P as a first-line therapy, with similar response rate.

Patients who relapsed following a response to first-line therapy had received a median of 19.8 (range 12-33) and of 17.1 (10-28) courses of MPH-P and PTC-VCR-P respectively. In patients who were primarily resistant, the corresponding figures were 12.1 (10-16) and 12.4 (8-16).

Response

Response was evaluated in 70/83 (85%) patients (Table II), including four patients (two from each arm) who died before

Table I Main clinical characteristics of patients with advanced multiple myeloma who were randomised to be treated, as third-line therapy, with the combination of epirubicin, prednisone and recombinant interferon-α2b (EPI-P-IFN) or with the combination of cyclophosphamide, prednisone and recombinant interferon-α2b (CTX-P-IFN)

	EPI-P-IFN	*CTX-P-IFN*	*Overall*
Number of patients	43	40	83
Male/Female	21/22	20/20	41/42
Median age (years) (range)	58 (46-75)	62 (44-79)	61 (44-79)
IgG	35	25	60
IgA	7	12	19
LC	1	3	4
K	26	25	51
L	17	15	32
β-2 $\mu g ml^{-1}$, median (range)	5.1 (1.4-13.7)	4.8 (2.1-11.3)	4.9 (1.4-13.7)
Lytic lesions			
0-3 (%)	6 (14)	9 (22)	15 (18)
>3 (%)	8 (19)	5 (13)	13 (16)
with pathological fractures (%)	29 (67)	26 (65)	55 (66)
Hb, $g dl^{-1}$			
>9	30	26	56
≤9	13	14	27
Serum creatinine, $mg dl^{-1}$			
≤2	41	39	80
>2	2	1	3
Prior first-line therapy			
MPH-P, no. of patients	30	33	63
PR+CR (%)	34	40	37
NR (%)	66	60	63
PTC-VCR-P, no. of patients	13	7	20
PR+CR (%)	54	43	50
NR (%)	46	57	50

MPH-P, melphalan-prednisone; PTC-VCR-P, peptichemio-vincristine-prednisone; PR, partial response; CR, complete response; NR, no response (stable+progressive disease).

Table II Response of patients with advanced multiple myeloma to the combination of epirubicin, prednisone and recombinant interferon-α2b (EPI-P-IFN) or to the combination of cyclophosphamide, prednisone and recombinant interferon-α2b (CTX-P-IFN)

	EPI-P-IFN	*CTX-P-IFN*	*Overall*
Evaluable patients	37	33	70
Relapsed patients[a]	14	13	27
Resistant patients[b]	23	20	43
CR+PR (%)	14/37 (38)	16/33 (48)	30/70 (43)
In relapsed patients (%)[a]	4/14 (28)	6/13 (46)	10/27 (37)
In resistant patients (%)[b]	10/23 (43)	10/20 (50)	20/43 (47)
PR (%)	8/37 (22)	13/33 (40)	21/70 (30)
CR (%)	6/37 (16)	3/33 (8)	9/70 (12)
SD (%)	16/37 (43)	13/33 (40)	29/70 (42)
PD (%)	7/37 (19)	4/33 (12)	11/70 (16)

[a]Relapsed patients are those patients who relapsed following a response to first-line therapy with MPH-P or with PTC-VCR-P. [b]Resistant patients are those patients who were primarily resistant to both MPH-P and PTC-VCR-P as first- and second-line therapies. PD, progressive disease (other abbreviations as in Table I)

response could be established and were considered as non-responders. Thirteen patients were not evaluated for refusal to continue treatment (four patients), insufficient data or lost to follow-up (nine patients).

The overall response rate was 43%, without statistical difference between the EPI-P-IFN (38%) and the CTX-P-IFN (48%) arm.

The response rate was similar in patients firstly treated with MPH-P and with PTC-VCR-P.

More responsive patients had WHO/ECOG performance status ameliorated (Table III), in a median time of 7 (range: 6-10) weeks in the EPI-P-IFN and of 10 (range: 6-12) weeks in the CTX-P-IFN arm.

Duration of response and of survival

The overall median duration of response was 5.9 months. It was similar in the EPI-P-IFN (5.5 months) and in the CTX-P-IFN (6.4 months) arm.

Table III Changes in WHO/ECOG performance status in responder patients with advanced multiple myeloma treated with third-line therapy (EPI-P-IFN or CTX-P-IFN)

WHO/ECOG performance status	*No. of patients*	
	Before therapy	*After therapy*
EPI-P-IFN arm (A)		
0-1	4	11
2	4	3
3	6	1
CTX-P-IFN arm (B)		
0-1	6	7
2	5	6
3	5	3
Arm A+Arm B		
0-1	10	18
2	9	9
3	11	4

(abbreviations as in Table I)

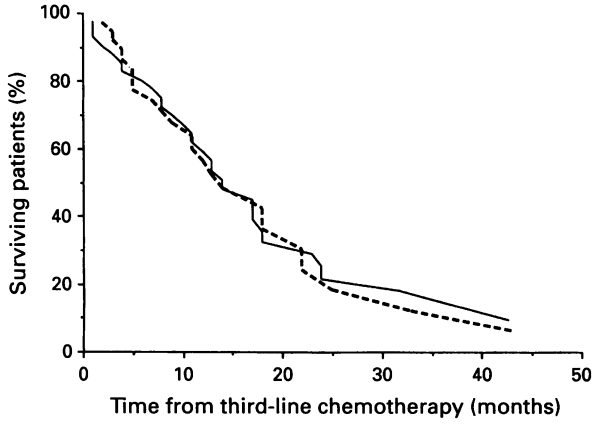

Figure 1 Duration of survival in MM patients who were randomised to be treated for third-line therapy with the combination of epirubicin, prednisone and interferon-α2b (EPI-P-IFN) (——) (33 patients, 13 censored) or with the combination of cyclophosphamide, prednisone and interferon-α2b (CTX-P-IFN) (- - - -) (30 patients, 17 censored). *P*-value, not significant.

Overall median survival was 14.1 months. It was similar in the EPI-P-IFN (13.9 months) and in the CTX-P-IFN (14.3 months) arm (Figure 1), as well as in patients who were primarily resistant to first-line therapy (15.0 months) and in those who relapsed following a response (13.4 months).

Toxicity

Overall haematological toxicity was low and 88% of courses were administered on an outpatient basis.

Febrile neutropenia occurred in 12% and grade III anaemia and thrombocytopenia in 7% and 5% of patients. These figures were somewhat but not significantly greater in the EPI-P-IFN than in the CTX-P-IFN arm (15%, 10% and 7% *vs* 6%, 4% and 2% respectively).

Grade 2-3 alopecia was distinctly more frequent in the EPI-P-IFN than in the CTX-P-IFN (55% *vs* 9%, $P<0.01$). Grade 2 emesis occurred in 20% and 9% (*P*-value not significant) of patients respectively. Stomatitis was unusual.

Four patients in both arms stopped IFN for grade 3 chills and/or fever, uncontrolled by acetaminophen premedications.

There was no cardiac damage attributable to EPI and no gastrointestinal, psychiatric or metabolic damage attributable to steroids.

Discussion

In this randomised study, patients with MM who were resistant to or relapsed following MPH-P and PTC-VCR-P achieved similar clinical benefit from being treated with EPI-P-IFN or CTX-P-IFN. In fact, response rate, changes in WHO/ECOG status and response and survival duration were similar with the two regimens.

These results are in keeping with published data on the value of CTX and anthracyclines for advanced MM. Used alone, CTX was effective in a number (Bersagel *et al.*, 1972; Brandes and Israels, 1987), although not in all (Presant and Klahr, 1978; Maclennan and Cuzick, 1985), non-randomised investigations. At present it is incorporated into regimens for refractory disease (Kyle *et al.*, 1975; Steinke *et al.*, 1985). Anthracyclines have not been used as a single agent. However, anthracycline-containing regimens are effective in both relapsed (Alexanian and Deeicer, 1984; Barlogie and Alexanian, 1987; Presant and Klahr, 1978) and primarily resistant (Cornelissen *et al.*, 1994) patients. The clinical role of IFN and steroids in favouring the effectiveness of both EPI and CTX cannot be established in this study.

As expected, haematological toxicity was low, non-haematological toxicity was acceptable and most patients were treated on an outpatient basis.

The overall 14.1 month median survival compares well with the median survivals of 5-22 months (the weighted median is about 10 months) reported in small non-randomised studies on salvage therapy in MM (Bonnet *et al.*, 1984; Lenhard *et al.*, 1984; Steinke *et al.*, 1985; Alexanian *et al.*, 1986; Forgeson *et al.*, 1988; Finnish Leukaemia Group, 1990; Friedenberg *et al.*, 1991; Gimsing *et al.*, 1991; Cornelissen *et al.*, 1994). These usually employed more cytotoxic drug combinations and often required hospitalisation. Median survival is also not better in young patients with advanced disease following autologous bone marrow (BM) or peripheral blood stem cell transplantation (Barlogie *et al.*, 1986; Fermand *et al.*, 1989).

In conclusion, it seems clinically acceptable to treat advanced MM with poorly myelosuppressive regimens based on medium doses of CTX or anthracyclines.

The following centres also participated in this study: Servizio di Oncologia, Ospedale S. Anna, 22100 Como (Dr C Epifani, Dr M Giordano); Divisione di Ematologia, Ospedale di Pesaro, 61100 Pesaro (Dr C Delfini); Medicina I, Ospedale di Alessandria (Dr G Montanaro, Dr A Pagetto); Medicina I, Ospedale di Melegnano (Professor G Santagati, Dr L Dezza); Medicina I, Ospedale di Gallarate (Dr A Ceriani, Dr R Castiglioni); Cattedra di Ematologia, Università di Parma (Professor V Rizzoli, Dr G Dotti); Medicina B, Ospedale di Biella (Professor S Fontana, Dr M Badone); Medicina Generale, Ospedale di Somma Lombardo (Professor M Mainardi, Dr A Daverio); Medicina C, Ospedale di Varese (Dr N Brumana); Medicina A, Ospedale di Varese (Dr G Pinotti).

Acknowledgements
Research supported by AIRC (Associazione Italiana per la Ricerca sul Cancro, Milano), by CNR (Consiglio Nazionale dell Ricerche, Roma, Progetto Finalizzato Applicazioni Cliniche della Ricerca Oncologica, grant no. 94. 01195 PF39), by IRCCS (Instituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia) and by MURST (Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Roma).

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