Eur J Cancer Clin Oncol, Vol. 20, No. 3, pp. 437–439, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Letter to the Editor

Multiple Myeloma with High Tumour Mass. Treatment with High-dose Methylprednisolone, Cyclophosphamide and Vindesine

O. A. VAN DOBBENBURGH,* M. R. HALIE,* H. PIERSMA,* J. MARRINK,† TH. OCKHUIZEN† and H. O. NIEWEG*

*Department of Medicine, Divisions of *Haematology and †Immunochemistry, University Hospital Groningen, Oostersingel 59, 9713 EZ Groningen, The Netherlands*

FROM cytokinetic studies performed in patients, it appears that the tritiated thymidine labelling index (LI) of newly diagnosed untreated myeloma is low, generally less than 3% [1, 2]. Treatment with alkylating agents results in a decrease of total body myeloma cell number (TBMC) with, in a proportion of patients, an increase in LI, especially in the first months of treatment [3, 4]. A considerable number of patients does not enter a stable plateau phase, but shows unstable disease with an increased LI, which is probably due to recruitment of resting (G_1) myeloma cells. Karp *et al.* showed that treatment with cyclophosphamide results in a humoral stimulatory activity (HSA), with a peak on the 9th day after cyclophosphamide administration [6]. This HSA, which could be a cause of the increased LI, increased tumour cell sensitivity to adriamycin [7]. Since vinca alkaloids are especially effective in proliferating cells, we considered it attractive to administer a vinca alkaloid 1 week after cyclophosphamide. In an effort to increase cell recruitment we used high-dose methylprednisolone administered concomitantly with the cyclophosphamide (high-dose methylprednisolone resulted in marked cell lysis and probable cell recruitment in aggressive non-Hodgkin's lymphoma; unpublished results).

Six untreated patients with a high TBMC (stage III, according to Durie and Salmon [8]) were treated with a regimen consisting of cyclophosphamide (C) 500 mg/m^2 i.v. and methylprednisolone (Solu-Medrol, S), 600 mg/m^2 i.v., both on day 1, and vindesine (Eldesine, E) 2 mg/m^2 i.v. on day 8 (day 1 = day 22, etc.). The patients all gave non-written informed consent. The aim was to induce a rapid tumour reduction and (by keeping the tumour mass in a low proliferating state by means of the vindesine) to prevent early relapses.

Determination of M-protein classes and subclasses, as well as determination of the Bence-Jones excretion, were done according to well-established methods. Clinical staging was done according to Durie and Salmon [8]. TBMC calculation and TBMC regression were estimated with the equations supplied by Salmon and Wampler [9]. For the patient with a Bence-Jones myeloma TBMC was not estimated. Response was evaluated according to the SWOG criteria [10]. Individual data are given in Table 1. Serial measurements of M-protein levels, TBMC and Bence-Jones excretion (patient 6) are given in Fig. 1. According to the SWOG criteria (Table 1), 2 patients were non-responders, 2 showed an improvement and 2 a partial response. In 4 patients a rapid decrease of TBMC resulted (patients 1, 2, 4 and 5), but in 2 of these (patients 1 and 4) rapid return of disease activity necessitated rescue therapy. Patients 3 and 6 showed a slow but continuous decline of TBMC. Toxicity of this CES regimen was negligible and consisted of occasional nausea, minimal hair-loss and sporadic leucopenia, the nadir being 2.1 × 10^9/l.

A few conclusions can be drawn from this pilot study. Since only 2 partial responses were observed, CES is probably not more effective than other regimens, although the observed minimal

Accepted 26 August 1983.

Table 1. Skeletal involvement, M-protein levels and total-body myeloma cell number (TBMC)

Patient, sex, age (yr)	M-type	Skeletal involvement*	Pretreatment M-protein (g/l) TBMC ($\times 10^{12}$)	Nadir M-protein (g/l) TBMC ($\times 10^{12}$)	Maximum decrease (in %) of M-protein and TBMC†	Response according to SWOG criteria	Follow-up‡
1. M.M. ♂ 65	A–K	lesions in skull, l + r humerus, fractures C4, Th 10, diffuse osteopenia	48.2 3.03	17.0 1.09	64.7 64.0	improvement	alive 42+ weeks, progressive disease after 6 × CES, stable on rescue therapy
2. A.H-R ♀ 64	G3–K	lesions in skull, left femur, C5, L5, large defect in pelvis	71.9 2.93	6.0 0.08	91.7 97.3	partial response	alive at 48+ weeks, Karn. 90, M-protein level stable 6–8 g/l
3. W.V. ♂ 36	G1–K	lesions in Th 1, 7, 8, 10, 11, L5 fractures C1, 3, 5 + multiple ribs	113.0 3.59	62.5 1.99	44.7 44.6	no response	alive 54+ weeks, Karn. 40–90
4. H.P. de G. ♀ 65	G1–K	diffuse osteopenia fracture L 1, 2, 3	67.6 2.37	36.7 1.11	45.7 53.1	no response	alive 61+ weeks, progressive disease after 6 × CES, stable on rescue therapy
5. H.N. ♂ 73	G1–λ	diffuse osteopenia lesions, left humerus and pelvis fracture Th 6, 7	58.3 2.30	20.0 0.6	65.7 73.9	improvement	died in week 17 of pneumonia after paraplegia due to spinal cord compression at Th 5
6. H. de W. ♂ 56	BJ–K	lesions in skull + left humerus fracture Th 4, 6	9.4 g/24 h light chain excretion	1.8 g/24 h light chain excretion	80.9	partial response	alive 66+ weeks, Karn. 50–90

*C, Th and L indicate cervical, thoracic and lumbar vertebrae.
†Decrease calculated in proportion to pretreatment values.
‡Karn. indicates Karnofsky score.

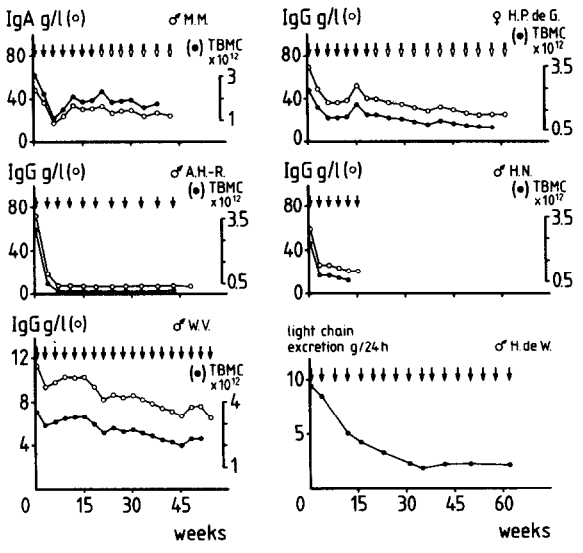

Fig. 1. Serial values of serum M-protein levels and TBMC (for patient 6 only light chain excretion is indicated; TBMC was not calculated). Patient H.N. died at week 17. ↓ indicates CES course, ↓ indicates rescue therapy.

toxicity should allow the use of higher doses. More disappointing was the occurrence of 2 early relapses, which we had hoped to prevent. In fact, the 3 types of reactions observed (slow TBMC reduction, rapid TBMC reduction and rapid TBMC reduction followed by rapid relapse) are the same as those observed by Durie *et al.* [5]. This indicates different tumour behaviour in a group of patients who are identical as far as TBMC is concerned. Whether this different behaviour is caused by really different kinetic properties or by different tumour-drug sensitivity remains to be established.

The different tumour behaviour was not abolished by our CES regimen. For really effective therapy it may be necessary to determine tumour kinetic data as well as tumour-drug sensitivity in every individual patient.

REFERENCES

1. DURIE BGM, SALMON SE, MOON TE. Pretreatment tumour mass, cell kinetics and prognosis in multiple myeloma. *Blood* 1980, **55**, 364–372.
2. DREWINKO B, ALEXANIAN R, BOYER H, BARLOGIE B, RUBINOW I. The growth fraction of multiple myeloma. *Blood* 1981, **57**, 333–338.
3. SALMON SE. Expansion of the growth fraction in multiple myeloma with alkylating agents. *Blood* 1975, **45**, 119–129.
4. DREWINKO B, BROWN BW, HUMPHREY R, ALEXANIAN R. Effect of chemotherapy on the labelling index of myeloma cells. *Cancer* 1974, **34**, 526–531.
5. DURIE BGM, RUSSELL DH, SALMON SE. Reappraisal of plateau phase in myeloma. *Lancet* 1980, 65–68.
6. KARP JE, BURKE PJ, HUMPHREY RL. Induction of serum stimulation and plasma cell proliferation during chemotherapy of multiple myeloma. *Blood* 1977, **49**, 925–934.
7. KARP JE, HUMPHREY RL, BURKE PJ. Timed sequential chemotherapy of cytoxan—refractory multiple myeloma with cytoxan and adriamycin based on induced tumour proliferation. *Blood* 1981, **57**, 468–475.
8. DURIE BGM, SALMON SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. *Cancer* 1975, **36**, 842–845.
9. SALMON SE, WAMPLER SB. Multiple myeloma: quantitative staging and assessment of response with a programmable pocket calculator. *Blood* 1977, **49**, 379–389.
10. BONNET J, ALEXANIAN R, SALMON S *et al.* Vincristine, BCNU, doxorubicin and prednisone (VBAP) combination in the treatment of relapsing multiple myeloma: a Southwest Oncology Group study. *Cancer Treat Rep* 1982, **66**, 1267–1271.