INSTITUTE OF ONCOLOGY, LJUBLJANA

TREATMENT OF REFRACTORY MYELOMA WITH HUMAN LEUKOCYTE INTERFERON ALPHA IN COMBINATION WITH HALF BODY IRRADIATION AND MELPHALAN — A CASE PRESENTATION

Plesničar A, Petrič G, Zwitter M, Jereb B

Abstract — A female patient with refractory myeloma progressing during third line chemotherapy, was treated with human leukocyte interferon in combination with half body irradiation and melphalan. After an objective response the disease has stabilized during 18 months from the start of the treatment. The combination of human leukocyte interferon and half body irradiation, together with chemotherapeutic agents, seems to be an encouraging approach to treatment of advanced refractory myeloma.

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Case report

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Introduction — Survival of patients with multiple myeloma has improved with the introduction of alkylating agents (usually melphalan or cyclophosphamide) and better supportive care. It has improved from a median of 7 months in the 1950 s to about 30 months at present (1). Nevertheless, in about 30 % to 50 % of patients we do not achieve a response with first treatment, and all of those who initially respond to standard treatment finally experience relapse. Reinduction therapy usually is of no effect (2, 3).

Options for patients with advanced and/or refractory myeloma include treatment with interferon or with systemic radiotherapy. Results of interferon therapy published in the late 1970 s and in the early 1980 s showed response rates between 8 % and 33 %. No clear difference in response rate was observed in patients with previously treated or untreated myeloma. The duration of response varied, from 1 to 25+ months (2, 4, 5). Whole body irradiation (WBI) and half body irradiation (HBI) have been used in the treatment of refractory myeloma since 1942. Relief of pain was reported in nearly all and objective responses in approximatelly one third of patients. The median survival of patients treated with WBI was 13 months and it was 11 months in patients treated with HBI (2, 6).

We report here on a female patient with multiple myeloma with progression of the disease during third line chemotherapy. She was then successfuly treated with a combination of human leukocyte interferon alpha (HLI-alpha), HBI and melphalan.

Methods — To identify the M-component in serum and in concentrated urine immune fixation after agarose electrophoresis was used. Serum albumin, alpha 1, alpha 2, beta and gamma globulin concentrations were determined by protein electrophoresis on celogel. Serum immunoglobulin (IgG, IgA, IgM) concentrations were determined immunochemically with laser nephelometry or with radial immunodiffusion. Bone marrow specimens were obtained by aspiration biopsies, plasma cells were determined according to the method described by Rohr (7).

The patient's disease was staged according to the system proposed by Durie and Salmon (8), clinical response was defined according to the criteria proposed by the Committee of the Chronic Leukemia Myeloma Task Force. For an »objective response« to therapy at least one of the following criteria has to be fulfilled: (a) $>50\,\%$ reduction in serum M-protein concentrations; (b) $>50\,\%$ reduction in urinary M-protein excre-

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tion; (c) 50 % decrease in cross-sectional area of a plasmacytoma; or (d) recalcification of bone lesions without development of new lesions.

HLI-alpha was supplied by Immunological Institute, Zagreb, Yugoslavia. It was given by intramuscular injection diluted in 5 milliliter distilled water. HBIs were delivered from a Cobalt source (Theratron 80, AECL), no shielding was used.

Case history — In September 1984 a 55 years old female was admitted to the Institute of Oncology, Ljubljana, Yugoslavia, because of 2 months long severe back pain, fever and weight loss. The results of the laboratory tests made at the time of admmission are shown in Table 1. IgG kappa was identified as serum M-protein, no Bence-Jones protein was found in urine. Bone marrow aspirate examination showed 113 plasma cells and 37 erythroblasts. Skeletal X-rays revealed osteolytic lesions in the skull, ribs, pelvis and spine. Her disease was staged as III A.

Tests	Results	Normal values
E.S.R. (mm/h)	80	0—15
Hb (g/L)	104	120—140
White cells ($\times 10^9$/L)	5.4	4.0—10.0
Thrombocytes ($\times 10^9$/L)	250	140—340
Serum albumin (g/L)	30.5	35—50
Serum alpha 1 glubulin (g/L)	5.9	1.6—3.4
Serum alpha 2 globulin (g/L)	5.4	4.5—8.5
Serum beta globulin (g/L)	11.4	5.4—10.0
Serum gamma globulin (g/L)	30.9	9.1—17.0
Serum IgG (g/L)	38.53	7.6—20.0
Serum IgA (g/L)	1.22	1.15—4.0
Serum IgM (g/L)	0.51	0.8—2.5
Serum creatinine (micromol/L)	68	71—106
Serum calcium (mmol/L)	2.5	2.1—2.6

Abbreviations:
E.S.R.: Erythrocyte sedimentation rate
Hb: Hemoglobin

Table 1 — Laboratory findings at the time of the first admission

Primary treatment consisted of systemic chemotherapy with melphalan and corticosteroids, irradiation of painful sites and HBI of 500 cGy to the upper and 300 cGy to the lower half of the body after 6 weeks interval. There was no objective response. In July 1986, 7 months after primary treatment, progression of the disease was observed. After treatment with cyclophosphamide, vincristine and corticosteroids, and then with third line chemotherapy consisting of vincristine, BCNU, adriamycin and corticosteroids (VBAP) the disease progressed continuously. After the third cycle of VBAP in July 1987 the patient was bedridden, with debilitating pain in the back and in both hips. Her performance status was 30 % according to Karnofsky scale. The treatment with intramuscular injections of $2{,}8 \times 10^6$ IU of HLI-alpha three times weekly was started. In the first and in the second week of treatment with HLI-alpha, the patient was additionally treated with HBI of the lower half of the body, each time with 250 cGy. No immediate side effects were noticed and pain relief occurred. In november 1987, after 3 months of continuous treatment with HLI-alpha toxic side effects were observed: Nausea, diarrheas, insomnia and fever. Therefore, HLI-alpha was given intermittently and combined with melphalan. Every 4 to 6 weeks the patient receives 2×10^6 IU of HLI-alpha for three days and then continues with melphalan in standard doses for four days.

Tests	Months after the start of the treatment with HLI-alpha, HBI and M										
	0	1	3	4	6	8	10	12	14	16	18
E.S.R.	36	—	65	65	77	65	57	44	53	33	48
Hb	115	126	101	115	109	108	112	121	121	133	140
White cells	4.6	4.4	2.6	3.1	2.6	4.3	3.7	3.2	2.3	2.8	3.1
Thrombocytes	287	257	242	232	177	176	193	234	225	257	299
Serum albumin	38.2	36.2	34.5	—	40.0	43.8	—	47.18	—	—	—
Serum IgG	22.62	—	25.84	—	24.31	25.42	21.64	—	25.68	—	—
Serum IgA	0.8	—	1.41	—	1.17	1.38	1.18	—	1.51	—	—
Serum IgM	0.36	—	0.66	—	0.78	0.69	0.65	—	0.79	—	—
Serum creatinine	92	77	104	—	—	92	104	106	—	—	—
Serum calcium	2.4	—	2.1	—	2.6	2.3	2.4	—	2.3	—	—
Myelogram											
Erythroblasts (cells/100L)	10	—	46	—	—	—	51.5	—	—	—	—
Plasma cells (cells/100L)	9	—	8	—	—	—	13	—	—	—	—

Abbreviations:
E.S.R.: Erythrocyte sedimentation rate
Hb: Hemoglobin
L: Leukopoietic cells
HLI-alpha: Human leukocyte interferon alpha
HBI: Half body irradiation
M: Melphalan

Table 2 — Laboratory findings after the start of the treatment with HLI-alpha and HBI (first three months) and later with HLI-alpha and M. For units and normal values see Table 1

In 18 months since the start of treatment with HLI-alpha in combination with HBI and melphalan objective response has been achieved. Remineralisation of the bone lesions in the pelvis was noticed in may 1988 and has continued until present. Both IgA and IgM have reached nearly normal levels and the results of other tests have improved (Table 2). Performance status has improved to 60%. The patient now walks with sticks and is hospitalized only during the applications of HLI-alpha and melphalan.

Discussion — After unsuccessful treatment with three different combinations of chemotherapy clinical response and stabilisation of multiple myeloma were achieved in our patient with HLI-alpha, HBI and melphalan. This remission is at present stable for 18 months, and the patient is alive 54 months from diagnosis. The results of treatment of refractory multiple myeloma with sequential HBI alone or HLI-alpha alone reported earlier, have not been very encouraging, the response rates were low and the durations of remissions short (2, 4, 5, 6). In our patient, in whom remission was achieved, the duration of the stable condition is longer than in similar patients treated with interferon or sequential HBI alone (10, 11). Even a change from progression to a static state has been considered a result (12). There is evidence for interferon to enhance the effect of irradiation as well as the effect of different chemotherapeutic agents (13, 14). It is therefore possible that treatment with combination of HLI-alpha, sequential HBI and melphalan in a larger group of patients with multiple myeloma would result in better remission rates and longer duration of remissions.

Povzetek

ZDRAVLJENJE REFRAKTARNEGA MIELOMA S HUMANIM LEVKOCITNIM INTERFERONOM ALFA V KOMBINACIJI Z OBSEVANJEM POLOVICE CELEGA TELESA IN MELFALANOM — PRIKAZ PRIMERA

Pri bolnici z refraktarnim mielomom je bolezen napredovala med zdravljenjem s sistemsko kemoterapijo tretjega reda. Zdravili smo jo s humanim levkocitnim interferonom alfa v kombinaciji z obsevanjem polovice celega telesa in melfalanom. Po objektivnem odgovoru je v 18 mesecih od začetka zdravljenja nastopila stabilizacija bolezni. Kombinacija humanega levkocitnega interferona z obsevanjem polovice telesa in melfalanom najverjetneje predstavlja nov možen način zdravljenja napredovalega refraktarnega mieloma.

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Author's adress: Plesničar A, MD, The Institute of Oncology, 61000 Ljubljana, Zaloška c. 2.