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Prospective Randomised Study of Double Hemi-body Irradiation With and Without Subsequent Maintenance Recombinant Alpha 2b Interferon on Survival in Patients with Relapsed Multiple Myeloma

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Immediately before first hemi-body irradiation, 59 patients with relapsed multiple myeloma were randomised to receive or not to receive subsequent alpha-2b interferon maintenance. 13 patients (22%) [8 of 31 (26%) controls, 5 of 28 (18%) in the interferon arm] received single hemi-body irradiation alone due to progressive disease and/or persistent cytopoenias following the initial procedure. Mean time between upper and lower hemi-body irradiation was 69 days (range 35–294). Of 23 patients randomised to receive interferon and completing double hemi-body irradiation, 15 (65%) achieved peripheral blood counts adequate to allow interferon administration as per study criteria commencing at a mean 116 days (61–241) from time of study entry. The mean period of interferon therapy, starting at a mean 65 days (26–160) post second hemi-body irradiation, is 16.4 months (2–33.5). There was no significant difference in median survival durations (10 months) from time of initial radiotherapy between control and interferon patients.
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INTRODUCTION

In 1971 Bergsagel suggested that systemic irradiation might be of value in the therapy of multiple myeloma [1]. He postulated that the relatively prolonged doubling time of the tumour might permit a high logarithmic cell kill with a clinically attainable radiation dose. The necessity for 'protection of the patient's marrow function' with such therapy was highlighted [1]. He proposed either division of total body irradiation (TBI) into two doses to allow repopulation of the irradiated marrow by circulating haemopoietic progenitor cells, or autologous bone marrow rescue from TBI. Currently, systemic radiation therapy in myelomatosis is indeed used either as part of a conditioning regimen pre allogeneic or autologous bone marrow transplantation or as a double hemi-body irradiation (DHBI) procedure [2].

Previous data on DHBI suggest that it is an effective modality of therapy in some patients with relapsed or resistant myelomatosis [2–10]. It has been suggested that DHBI gives a more durable response in these patients than a single hemi-body (HBI) procedure [2, 3]. This claim is based on a comparison of response rates and median survival times of patients receiving either HBI or DHBI in single-arm retrospective studies. The degree to which the initially administered HBI had acted as a 'screening' procedure is, therefore, difficult to assess. Survival for sufficient time to attain a haematological, biochemical and clinical state adequate to undergo the second HBI might well represent inadvertent selection of relatively good prognosis patients.

Also, it is recognised increasingly that in the assessment of therapeutic response it is necessary to distinguish between patients primarily resistant to cytotoxic therapy and those who relapse following initial response [11, 12]. This distinction has rarely been made in previous reports on DHBI therapy of myelomatosis. For these reasons we initiated a prospective study of DHBI therapy in a population of patients with relapsed post-plateau phase myelomatosis. DHBI has a limited ability to prolong life in relapse patients [3]. Many will have a compromised marrow reserve before and after the procedure. This limits the extent to which necessary adjuvant therapy can be given. Initial evidence of the efficacy of alpha interferon in resistant myelomatosis and its favourable side-effect profile [13] prompted the following study design.

PATIENTS AND METHODS

Patients were prospectively randomised prior to receipt of initial HBI to receive, post their second HBI, supportive care plus alpha-2b interferon (Intron) or supportive care only. All patients received irradiation initially to either upper or lower hemi-body fields as dictated by sites of maximum bone pain. All irradiation was admininstered from a slow cobalt source as previously described [3]. Both first and second HBIs were

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administered when the peripheral absolute neutrophil count was greater than 10^9/l and the peripheral platelet count was greater than 100×10^9/l. A dose of 7.5 Gy was given to the upper body at a source to skin distance of 200 cm. Lung shielding and lung correction were not employed, and total treatment time was approximately 50 min. Patients were treated with a single large opposed field (anterior and posterior). The UHBI field used in the early part of the study extended from the lower border of the mandible, with the head fully extended, to the umbilicus. This field was later extended to include the skull in 18 patients. Patients undergoing UHBI were fasted for 6 h prior to the procedure. Lower hemi-body irradiation (LHBI) was administered in a similar manner at a dose of 10 Gy to a field extending from umbilicus to ankles. Premedication was routinely used, consisting of bolus intravenous doses of lorazepam and metoclopramide with dexamethasone (8 mg orally).

The study interferon regimen was 3 MU of recombinant alpha 2b interferon (Intron) administered subcutaneously three times per week. This was commenced when the peripheral total white cell count was greater than 10^9/l and the peripheral platelet count was greater than 100×10^9/l. Paracetamol was prescribed to a maximum dose of 500 mg four times daily to alleviate influenza-like side-effects. Patients were encouraged to self-administer interferon in the evening to reduce side-effects. The use of prostaglandin inhibitors, such as aspirin or indomethacin, was not allowed. Concomitant medications were kept to an absolute minimum and dosages held constant, as far as possible, during the entire study period. Clinical, haematological and biochemical assessments were carried out weekly during the DHBI procedure and for the first month of alpha interferon therapy and at a minimum of once every 6 weeks thereafter. Skeletal surveys were carried out in all patients pre-DHBI and at subsequent 6-month intervals.

This protocol received local ethical committee approval and fully informed consent was obtained from all patients prior to study entry. Study end point was survival from time of receipt of first HBI and was estimated using the Kaplan–Meier method with comparisons using the log-rank test.

Patients

59 patients sequentially referred for therapy of relapsed multiple myeloma were entered on this study. Patient characteristics at time of study entry are shown in Table 1. All patients fulfilled study criteria for diagnosis of multiple myeloma, plateau phase and relapse. Multiple myeloma was diagnosed on the basis of a quantifiable level of paraprotein in serum and/or urine and either of the following: (a) a bone marrow infiltrate of > 20% plasma cells or microplasmacytomas on marrow section or smears, or (b) lytic bone lesions. Patients were accepted as being in plateau phase when the following criteria were satisfied: minimal or no symptoms attributable to active disease, transfusion independent and serum paraprotein, urinary light chain output and serum beta$_2$ microglobulin levels had become stable as assessed on two samples taken at an interval of 2 months. Relapse of disease was defined as a 50% or greater increase in serum and/or urine paraprotein levels above that of the plateau phase.

Table 1. Patient details at time of study entry and patient therapy/plateau details

	Interferon (n = 28)	Control (n = 31)
Sex (M/F)	14/14	18/13
Age [Years mean (range)]	67 (47–83)	66 (49–81)
Paraprotein type		
IgG k/l	15	18
IgA k/l	6	7
kappa	4	3
lambda	3	2
IgD kappa		1
Durie-Salmon stage		
II	6	7
III	22	24
Urinary Bence-Jones protein positive	15	14
Haemoglobin [g/dl mean (range)]	11.2 (9–14)	11.3 (7–14)
White cells [$\times 10^9$/l mean (range)]	5.9 (1–12)	4.7 (2–10)
Platelets [$\times 10^9$/l mean (range)]	246 (68–424)	177 (47–489)
Urea [mmol/l mean (range)]	7.2 (3.1–24.4)	7.1 (4.1–11.9)
Creatinine [μmol/l mean (range)]	119 (61–440)	123 (53–440)
Albumin [g/l mean (range)]	39.6 (3–48)	37.6 (29–52)
Calcium [mmol/l mean (range)]	2.5 (2.08–4.40)	2.42 (2.0–2.83)
Beat-2 microglobulin		
Serum [mg/l mean (range)]	6.9 (1.6–25)	8 (2.3–66)
24-h urinary [mg mean (range)]	15.9 (0–107)	14.2 (0–17)
Induction therapy at diagnosis		
Melphalan/prednisone	16	26
VAD	9	2
ABCM	1	1
Other	2	2
2 regimens used in induction phase	7	5
3 regimens used in induction phase	1	0
Chemotherapy given at relapse	12	13
Melphalan/prednisone	5	4
VAD	3	2
Other	4	7
DHBI as first-line relapse therapy	16	18
Plateau duration (months mean/range)	9.6 (4–22)	9.8 (3–21)

RESULTS

59 patients were entered on the study between 1 April 1987 and 1 June 1990. It was intended that all patients receive double hemi-body irradiation. 28 patients (47%) were randomised to receive supportive care plus interferon while 31 (53%) were randomised to receive supportive care only. 13 patients [8 of 31 (26%) in the control arm, 5 of 28 (18%) in the interferon arm] received single hemi-body irradiation alone due to progressive disease and/or persistent cytopenias following the initial procedure. Median survival in patients receiving single HBI was 3 months in both study arms. Baseline peripheral blood counts, degree of marrow plasma cell infiltrate, paraprotein type or amount, duration of plateau phase, type(s) of prior chemotherapy either as induction or at time of relapse (MP vs. VAD vs. ABCM vs. other regimens), amount of prior chemotherapy received at time of induction or at time of relapse or receipt of DHBI as first-line or post-chemotherapy relapse therapy did not predict those patients who would prove unfit for second HBI or significantly affect survival in the study cohort of patients. 3 patients who had received HBI lived for more than 6 months

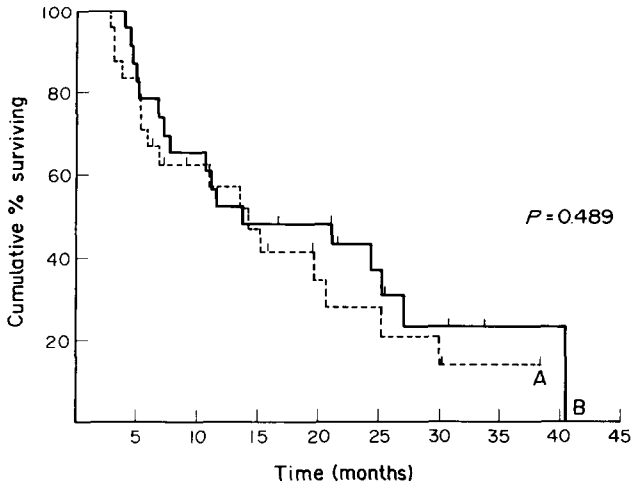

Fig. 1. Median survival from time of first HBI in 23 control DHBI patients (A) vs. 23 DHBI patients randomised to alpha-2B interferon therapy postDHBI (B).

from the procedure, 1 patient for 11 months with 2 patients in ongoing second plateau phase of disease for 13 and 37 months, respectively.

46 patients received DHBI, 23 in the control arm, 23 in the interferon arm. 15 of this latter group of patients achieved peripheral blood counts adequate to allow interferon administration. Receipt or non-receipt of skull radiation had no significant impact on survival. The remaining 8 patients were persistently cytopenic postDHBI and had a median survival of 6 months. Those patients receiving interferon postDHBI had a median survival of 26 months but these represent a highly selected group of patients. This median survival did not differ significantly from that in those 14 patients in the control group who achieved peripheral blood counts adequate to receive interferon had they been so randomised. The mean period of interferon therapy postDHBI was 16.4 months (2–33.5 months).

The median survival in all 46 patients receiving DHBI was 15 months and was equivalent in both study arms (Fig. 1). Of these patients achieved a greater than 50% decrement in paraprotein levels postDHBI. 2 of 9 patients receiving interferon therapy had reversal of baseline subnormal IgA and IgM levels after 1 year of maintenance therapy, this was not seen in any of 8 equivalent patients in the control group.

Toxicity

All 54 patients receiving UHBI experienced transient nausea, vomiting and anorexia. Those patients receiving skull radiation suffered transient alopecia and oral mucositis. 1 patient was clinically diagnosed as having radiation-induced pneumonitis which responded promptly to oral corticosteroid therapy. Pneumonitis may also have occurred in a further 4 patients who died from respiratory failure secondary to lower respiratory tract infections while cytopoenic postUHBI. All 50 patients receiving LHBI experienced transient nausea, vomiting, anorexia and diarrhoea. Radiation dermatitis of the scrotal area occurred in 2 patients. The mean time to achievement of a peripheral blood total white cell count of 10^9/l and a platelet count of 100×10^9/l postDHBI was 3.3 months (range 2–6). All patients receiving either HBI or DHBI required red cell transfusion support (mean 8 units, range 4–36). One third of all patients required platelet transfusion support postDHBI (mean 54 units, range 12–360). All patients experienced transient influenza-like symptoms soon after initiation of alpha-interferon therapy. These consisted of WHO Grade 1 fever, myalgia, arthralgia and lethargy which lasted for a mean of 3 days (range 1–7 days). Symptoms were significantly alleviated in most patients by oral paracetamol. Three patients developed hypothyroidism while on interferon therapy post DHBI, this was not seen in any patient in the control arm. Transient mild elevation in hepatic transaminases were recorded in 13 of 15 patients immediately postinitiation of interferon therapy.

DISCUSSION

The vast majority of patients who relapse from plateau have drug-resistant disease (as evidenced by the very low response rates to most combination cytotoxic regimens) and suffer poor quality of life and short survival durations following available relapse regimens [11]. All patients on study had relapsed multiple myeloma and many had failed second or third line therapy. The rationale for introduction of systemic radiotherapy in drug-resistant myelomatosis is based on the lack of resistance to radiotherapy at a cell membrane level. It is thus hoped that radiotherapy may be efffective even in alkylating agent-resistant myelomatosis.

DHBI is administered in the hope that the marrow reserve in the unirradiated half of the body will be sufficient to maintain safe peripheral blood cell levels. Haemopoietic cells originating in the untreated marrow may also contribute to marrow reconstitution within the radiation field. A deleterious effect attributable to reseeding of the irradiated marrow by circulating malignant cells has not been demonstrated but is a concern as circulating myeloma progenitors have been demonstrated in myeloma patients [14].

Cytopenias postHBI and postDHBI were very significant clinical problems in this study population. These problems have also recently been highlighted in data from a SWOG study investigating the use of DHBI as consolidation therapy following combination cytotoxic induction therapy or as second line therapy in partial or non-responding patients [15]. 22% of the presently reported patient cohort were unable to have both HBI procedures, while a further 32% suffered prolonged cytopoenias postDHBI of sufficient severity to render it impossible to administer even gentle adjuvant therapy. It was thus not possible to fully assess the role of low dose alpha 2b interferon in this model. The restoration from base-line subnormal levels of serum immunoglobulins noted in 2 patients in the interferon study arm confirms previous similar data previously noted where recombinant alpha interferon has been used as a single agent in both newly presenting and chemo-resistant patients [16].

Previous reports have emphasized the risk of radiation-associated pneumonitis following UHBI, especially in patients with intra-thoracic metastases [17]. The difficulties of establishing this diagnosis in neutropenic patients with overt lower respiratory tract infections postUHBI have previously been highlighted [7].

It is generally accepted that a dose of 8 Gy of ^{60}cobalt-source UHBI can be given, in the absence of previous pulmonary damage or concurrent major pulmonary irradiation procedures, with a minimum risk of subsequent pneumonitis [18]. 1 patient, out of a total of 54 receiving UHBI, was clinically diagnosed as having steroid-responsive radiation-induced pneumonitis while pneumonitis may also have occurred in a further 4 neutropenic patients who died from respiratory failure secondary to lower respiratory tract infections postUHBI. These data are consistent with previously documented incidences of this complication in

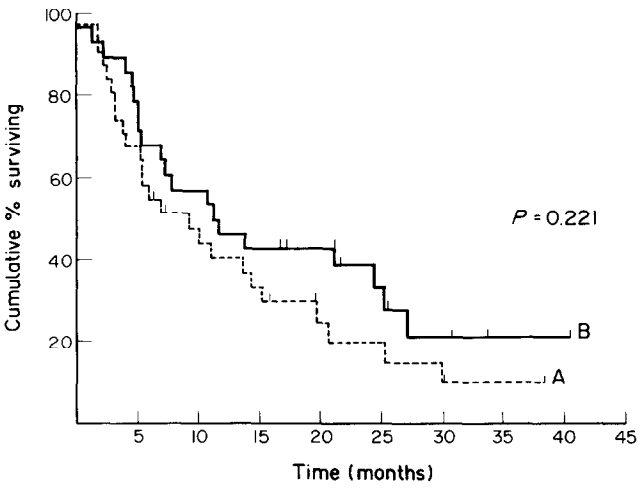

Fig. 2. Median survival from time of first HBI in 31 patients randomised to control arm (A) vs. 28 patients randomised to receive interferon postDHBI (B).

patients with advanced neoplastic disease receiving UHBI [19]. We have previously documented significant abnormalities in base-line pulmonary function tests in patients about to receive UHBI [20]. This may be due to prior chemotherapy and/or recurrent lower respiratory tract infections associated with these patient's immunocompromised state. Future studies involving UHBI therapy should incorporate sequential pulmonary-function tests with appropriate use of dose-reduction and/or lung-shielding as deemed necessary.

Median survival in the study cohort was 10 months with no evident effect of postDHBI alpha interferon maintenance therapy (Fig. 2). Very few prospective therapeutic studies which quote median survival times in patients with relapsed myelomatosis have been published [11]. The current scanty data would suggest that few regimens offer a median survival time of 1 year in this patient population [11]. A prospective randomised study of DHBI vs. other relapse regimens is thus indicated.

The need to irradiate the entire skeleton as part of the DHBI procedure became evident as this study progressed. Rapid development of myelomatous bone and soft tissue lesions occurred, in areas excluded from the initial radiation fields, in at least 5 patients on the study [21]. The precise DHBI technique used significantly affects the subsequent behavior of the disease. An accurate assessment of the nature and distribution of relapse postsystemic irradiation must be made. Standardisation of the DHBI technique should be implemented to allow valid comparison of clinical studies.

A thrice weekly 3 Mu alpha-2b interferon regimen was very well tolerated by patients on study. From this study data, it may be expected that approximately half of patients with advanced multiple myeloma will be eligible to receive this therapy following DHBI. The study alpha-2b interferon regimen has recently been shown to prolong survival if given as maintenance therapy to those achieving a good response to induction cytotoxic therapy [22]. Data from this study would also suggest that the survival benefit conferred by alpha interferon therapy is still present and on-going at time of disease relapse [22]. Confirmation of this data is now being sought in a number of studies. As we have no evidence that any procedure is curative in advanced myelomatosis, evidence from the currently reported study that maintenance interferon therapy can be given postDHBI is thus important. Recombinant alpha interferon is an effective agent in relapsed/refractory myeloma [23]. Inclusion of larger numbers of patients with relapsed myelomatosis in a prospective study, possibly incorporating recombinant growth factors into the systemic radiotherapy regimen, may allow a full assessment of the potential role of recombinant alpha interferon in this context.

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