



Acute lymphoblastic leukaemia-type intensive chemotherapy to eliminate minimal residual disease after high-dose melphalan and autologous transplantation in multiple myeloma – a phase I/II feasibility and tolerance study of 17 patients

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Summary:

Aiming to target the minimal residual disease in patients with multiple myeloma, a phase I/II single centre study was undertaken for feasibility and tolerance of intensive acute lymphoblastic leukaemia consolidation chemotherapy (ALL-IC) as part of a strategy for post-transplant consolidation targeted at pre-B cells. Seventeen newly diagnosed patients with myeloma (median age 55 years; 30–65) were initially treated with courses of infused cyclophosphamide, vincristine, adriamycin and methylprednisolone (C-VAMP) followed by melphalan 200 mg/m² (HDM) and peripheral blood stem cell rescue (PBSC). Forty-seven percent were in CR and the rest in PR after HDM. ALL-IC consisted of vincristine, daunorubicin, etoposide, cytarabine, 6-thioguanine and prednisolone given over 5 days. All patients became neutropenic ($<0.5 \times 10^9/l$) at a median of 10 days (4–18) and one of the 17 patients (5.8%) died 15 days post ALL-IC of sepsis. A further four have died of relapse with an overall survival (OS) of 67% at 4 years. Two of nine patients in PR at the time of ALL-IC achieved CR. Matched-pair analysis of 34 control patients shows no difference for OS and event-free survival between ALL-IC and controls. We conclude that ALL-IC given to myeloma patients after HDM/PBSC is as safe as when used in ALL and warrants further assessment in randomised trials for myeloma. *Bone Marrow Transplantation* (2000) 25, 949–956.

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by intensive chemotherapy usually with an alkylating agent such as melphalan² with stem cell rescue using either previously harvested autologous marrow (ABMT)³ or G-CSF-generated peripheral blood stem cells (PBSC).⁴ This treatment has been shown to be beneficial in randomised controlled trials.⁵ More recently, patients have also been shown to obtain survival benefit if after this intensive treatment they are then given long-term maintenance interferon (IFN).⁶ All this treatment together^{7,8} results in high complete remission (CR) rates of greater than 50% for new unselected patients, with a median overall survival of 4.5 years. For those who are in CR and received IFN a median overall survival has not yet been reached after more than 8 years.

Eventually all patients with myeloma relapse and die, perhaps in part due to the reinfusion of unpurged tainted marrow after the high-dose treatment but also because of persistent minimal residual disease (MRD) in the patient. Studies looking at patients in complete remission with myeloma indicate that at a molecular level all patients still have significant amounts of residual myeloma.⁹ We have previously addressed this problem following autografts for CR patients in acute lymphoblastic leukaemia (ALL), and have shown the benefit of maintenance chemotherapy with 6-mercaptopurine and methotrexate in this setting.¹⁰

The present study was therefore designed to see if, in myeloma, intensive combination chemotherapy given after the autologous bone marrow transplant may be a strategy for attempting to obtain cure for these patients.

The exact nature of the intensive chemotherapy that we have used in this study is based upon the increasing evidence that in complete remission the phenotype of the myeloma stem cell is consistent with it being of pre-B origin,^{11,12} ie similar to that seen in ALL. We have therefore used the sort of intensive chemotherapy used to consolidate high risk acute lymphoblastic leukaemia (ALL) after attaining complete remission.¹³ The aim of this block of treatment is to target the pre-B stem cells during remission and this is known to be effective in ALL. The programme we have chosen is the post-remission week 5 or week 20 intensification block of chemotherapy used in the MRC UKALL XA study for acute lymphoblastic leukaemia.¹³ We have extensive experience of using this block of treatment in adult leukaemia¹⁴ and this study has been designed to assess its feasibility and tolerance when used shortly

The modern treatment of new patients with myeloma under the age of 75 years is increasingly involving initial courses of infusional chemotherapy with vincristine, an anthracycline and steroids (ie the C-VAMP programme)¹ followed

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after an autologous bone marrow transplant in myeloma, at a time similar to that in ALL when patients have had complete or near complete responses.

The results presented here are an extension of an early preliminary presentation¹⁵ and analyse the feasibility and tolerance of this chemotherapy. Comparison with matched pairs not receiving ALL-IC obtained from the prospective Royal Marsden database has also been undertaken to determine the significance of early toxicity.

Materials and methods

Patients

Between October 1995 and April 1998, 17 patients with myeloma currently being treated at the Royal Marsden Hospital received ALL-IC. Their details and demography are shown in Table 1. All patients had received induction chemotherapy (see below) followed by an autologous transplant and were in CR or stable plateau phase, aged less than 70 years, and with a WHO performance status of 0, 1 or 2. They were not eligible for allogeneic bone marrow transplant, and had a glomerular filtration rate (GFR) by ⁵¹Cr EDTA of >30 ml/min. All gave informed consent for patient participation in a protocol approved by the Royal Marsden NHS Trust Committee for Clinical Research.

Treatment

Induction chemotherapy: C-VAMP¹: All patients received courses of C-VAMP consisting of vincristine 0.4 mg per day i.v. by continuous infusion for 4 days, doxorubicin 9 mg/m²/day i.v. by continuous infusion for 4 days, and

methylprednisolone 1.5 g i.v. or p.o. for 4 days and then tapered, and weekly cyclophosphamide 500 mg i.v. on days 1, 8 and 15. All courses in these programmes were repeated every 21 days until maximum response. One further course was then given. If chemotherapy was compromised by bone marrow failure, doses of cyclophosphamide were omitted rather than delaying VAMP therapy.

High-dose treatment: Approximately 6 weeks after the start of the last chemotherapy cycle, high-dose treatment was given consisting of melphalan (200 mg/m² infusion over 30 min) on day -1 if GFR was >40 ml/min.³ Adequate hydration before and after high-dose treatment with melphalan was ensured to maintain a urine output of 20 ml/min 1 h after the high dose and 500 ml/h in the subsequent 2 h.

Peripheral blood stem cell transplants (PBSCT): All patients received PBSCTs using stem cells mobilized approximately 6 weeks after the last chemotherapy cycle⁴ using recombinant human granulocyte colony-stimulating factor (rhG-CSF) (Amgen, Thousand Oaks, CA, USA), all harvests being undertaken as an outpatient procedure using the Cobe separator (Cobe, Denver, CO, USA). Stem cells were stored following controlled cooling with 5% dimethylsulphoxide (DMSO) at -179°C in the vapour phase of liquid nitrogen. When required, it was rapidly thawed at 37°C and reinfused immediately without further processing. The median mononuclear cell dose returned was 7.07 × 10⁸/kg.

Maintenance interferon (IFN): After high-dose treatment, some patients were started on maintenance interferon alpha

Table 1 Demography of patients and response after various phases of treatment

Case No.	Age (years)	Class of PP	Stage	No. of CVAMP	Status after CVAMP	Status after Auto	Time from Auto-UKALL (months)	Days in hospital	Status after UKALL	Months after UKALL A/D	Start of IFN (months)	Alive/Dead	β ₂ M (μg/ml)
1	49	NS	IA	6	PR	CR	12.0	17	CR	35.5	4.5	A	2.2
2	53	IgGK	IIIA	5	PR	CR	5.5	14	CR	40.5	2.0	A	2.0
3	50	IgAL	IIIB	4	PR	PR	3.0	22	PR	19.0	1.5	A	48.6
4	51	IgGL	IIIA	6	PR	PR	9.0	6	PR	41.0	1.5	A	3.8
5	59	IgGK	IIIA	7	PR	PR	11.5	16	NR	19.8	2.0	D	4.9
6 ^{a,b}	62	IgGL	IIIA	6	PR	PR	3.0	14	NR	8.7	1.5	D	6.0
7	56	IgGK	IIIB	4	PR	CR	6.0	19	CR	40.0	1.0	A	5.8
8	55	IgAK	IIA	5	PR	PR	3.0	25	PR	35.0	1.0	D	2.8
9	64	IgGK/L	IIIA	6	CR	CR	3.0	23	CR	34.0	2.0	A	2.9
10	61	BJK	IIIA	6	PR	CR	10.0	23	CR	112.5	2.5	A	3.8
11 ^{a,c}	30	IgGK	IIIA	7	PR	PR	1.5	27	CR	30.0	3.0	A	3.7
12	57	IgGK	IIIA	8	PR	CR	5.5	20	CR	25.5	3.5	D	4.3
13 ^{a,d}	63	IgGK	IIIA	6	PR	PR	17.5	17	PR	35.5	—	A	1.8
14	50	IgGK	IIIA	6	PR	PR	11.0	15	PR	34.0	1.5	A	4.0
15	47	BJL	IA	6	PR	CR	10.0	13	CR	37.0	11.0	A	1.4
16	43	IgGK	IIIA	6	NR	PR	6.0	17	CR	41.0	3.0	A	1.8
17	65	IgGK	IIIA	8	CR	CR	7.0	15	NE	—	—	D	3.7

(died)

^aPatients who received less than 3 months chemotherapy prior to C-VAMP.

^bABCM – three cycles.

^cOral melphalan + cyclophosphamide + dexamethasone alternating with interferon – one cycle.

^dOral melphalan – prednisolone – two cycles.

(3 mega units/m² 3 × weekly, S/C-Schering Plough, Welwyn Garden City, UK) initially as part of a randomised trial^{3,16,17} and subsequently in all patients when the WBC count reached 2 × 10⁹/l and platelet count 50 × 10⁹/l. The dose of interferon was reduced or stopped according to haematological criteria or other toxic manifestations.

ALL-IC: Seventeen patients received ALL-IC. The ALL-IC consisted of vincristine 1.5 mg/m² i.v. day 1 (maximum 2 mg), daunorubicin 45 mg/m² i.v. on days 1–2, etoposide 100 mg/m² i.v. days 1–5, cytarabine 100 mg/m² every 12 h i.v. days 1–5, 6-thioguanine 80 mg/m² p.o. days 1–5 and prednisolone 40 mg/m² p.o. days 1–7 and it was then tapered over days 8–14.

Investigations

Pre-treatment evaluation included complete blood counts and chemistry, a serum and urine protein immune electrophoresis was done on cellulose acetate membranes followed by immunofixation, and serum levels of immunoglobulins and β₂ microglobulin (β₂M). Every patient had a bone marrow aspirate and a trephine biopsy and a full radiological skeletal survey prior to treatment as part of restaging. The staging was done according to the Durie and Salmon¹⁸ system. Full blood counts and biochemistry were done every day during hospitalisation and were repeated weekly thereafter. The paraprotein studies were done every three weeks throughout the treatment. Restaging with bone marrow examinations and radiological assessments were carried out after plateauing of paraprotein, or after maximum response.

Supportive treatment

Neutropenic sepsis was treated with standard intravenous broad-spectrum antibiotics according to our hospital guidelines as in-patients, but otherwise there was no use of systemic prophylactic antibacterial, antifungal or antiviral antibiotics. Haemopoietic growth factors were not used prophylactically but in one patient (No. 17) Filgrastim (G-CSF) was started the day he died, 15 days after starting ALL-IC, because he failed to engraft and was septicaemic (see below). For the administration of ALL-IC all the patients were admitted to a four-bedded ward and were nursed without barrier nursing or filtered air. Packed cells and platelets were transfused to keep the haemoglobin >9 g/dl and platelets >10 × 10⁹/l in afebrile patients, and a platelet count of >20 × 10⁹/l in febrile patients. Gut antimicrobial prophylaxis was not used in the patients. They were encouraged to have a normal diet and mouth care included mouthwashes and Nystatin suspension or amphotericin lozenges.

Assessment of toxicity

Toxicity was assessed according to WHO criteria and the variables analysed were days of hospitalisation, nausea, vomiting, mucositis, diarrhoea, constipation, anorexia, alopecia, infection, cutaneous toxicity, haematological toxicity, hepato-toxicity (serum bilirubin, alanine, amino trans-

aminase, alkaline phosphatase), and nephrotoxicity (serum creatinine).

Criteria for response

We used the same criteria for response as previously described.¹⁹ Four criteria had to be met for a patient to be regarded as having achieved CR: (1) no paraprotein measurable by scanning densitometry of serum proteins separated on cellulose acetate membrane by electrophoresis and stained with Ponceau S and immunofixed with Nigrosin;^{20,21} (2) no detectable Bence Jones proteinuria on electrophoresis of neat urine stained with colloidal gold and immunofixed with Nigrosin; (3) 5% or fewer plasma cells of normal morphology on bone marrow aspiration; and (4) criteria 1–3 had to be fulfilled for at least 3 months without evidence of extramedullary disease. Patients were regarded as having achieved a partial response (PR) if there was a 50% decrease in measurable paraprotein (IgG or IgA myeloma) or bone marrow infiltration (non-secretory or Bence Jones myeloma) which was sustained for a month or more.

Selection of matched controls

The 34 matched control patients were selected by using in-house computer routines similar to minimum distance case-control matching, ie a Euclidian distance measure method.²² From the RMH prospective database of 712 myeloma patients, 106 were selected who had received C-VAMP as their first treatment, followed by HDM/PBSC and no ALL-IC. From these 106 patients, two matched patients for each of the 17 ALL-IC patients were identified at random as follows: (a) myeloma isotype, (b) stage at presentation, (c) time period from diagnosis to ALL-IC (d) disease status at ALL-IC or that at 'an equivalent duration' (ie up to ALL-IC) (d) number of courses of C-VAMP, <5 or ≥ 5, (e) interferon before ALL-IC. Each pair of matched patients chosen were those with the best match in the order (a) to (e). Where there were more than two possible matches after a full (a) to (e) agreement, the two closest patient numbers were chosen (equivalent to closest registration dates). Because time censoring effect biases outcome we have constructed our matched pair analysis so that the closest match is at least 6 months post autograft, accounting for the time lag between autograft and ALL-IC (median 6 months, range 1.5–17.5).

Statistical considerations

Analysis was undertaken in May 1999. Patient characteristics at presentation were compared using the chi-square test for categoric data and the Kruskal–Wallis²³ non-parametric test for numeric data. Overall survival (OS) and event-free survival (EFS) curves were produced using the Kaplan–Meier²⁴ method from the date of diagnosis and from ALL-IC and the comparison between curves was carried out using the log rank test.²⁵ An event was defined as the occurrence of death or relapse.

Results

Patient characteristics

Table 1 shows the individual demography and outcome of the 17 patients included in the study. The median age was 55 (range 30–65 years) and 14 of the 17 patients were stage IIIA/B at presentation. The median β_2 M was 3.7 μ g/ml (1.4–48.6) at diagnosis which is quite modest for active myeloma. Only one of our patients had a β_2 M more than 6 μ g/ml. The median time between autograft and ALL-IC was 6 (1.5–17.5) months.

Response prior to ALL-IC

For all the patients the ALL-IC represented the final stage of their consolidation during their initial treatment. Three of these patients (Nos 6, 11, 13) had minor treatment prior to embarking on the total therapy (see Table 1). For all 17 patients receiving total therapy the median number of courses of C-VAMPs was 6 (range 4–8). The response to this initial infusional chemotherapy was two CR (11.7%), one non-responder (5.9%) and all the rest attained PR (82.4%). After high-dose melphalan stem cell transplants eight (47.1%) patients were in complete remission and nine in partial remission.

ALL-IC protocol compliance

All patients received the drugs in planned scheduled doses. There were no protocol violations. One patient failed to engraft and died (No. 17) on day +15 post ALL-IC.

Haematology

Neutropenia: All patients had grade 3 to 4 neutropenia after ALL-IC. The median number of days of neutrophils of less than $0.5 \times 10^9/l$ was 10 days (4–18).

Thrombocytopenia: The median number of days below $50 \times 10^9/l$ was 14 days (2–77) with all patients dropping below $50 \times 10^9/l$.

Haemopoietic support: Packed red cells were given to 12/17 patients with a median number of 3 units (0–5). Platelet transfusions were given to 16/17 patients on a median of two occasions (0–9) but six patients had still not recovered platelet counts of $>100 \times 10^9/l$, 30 days after ALL-IC.

Hospital admission days: All patients were admitted for the 5 days of ALL-IC and 13/17 (76.5%) went home within 7 days. Barring one, all (12/13) patients were rehospitalised in the second or third week with febrile neutropenia. The median number of days in hospital for ALL-IC was 17 (6–27).

Antibiotic sepsis support

One patient did not require parenteral antibiotics at any time after ALL-IC. The median number of days for intra-

venous antibiotics was 9 (0–16). Five patients needed parenteral antifungal treatment for presumed systemic fungal infection. One patient died on day 15 of neutropenic sepsis (see below).

WHO toxicity other than haematological

Eight of 17 (47.1%) patients had grade III/IV toxicity due to infection 2–4 weeks after ALL-IC, the majority being in the second week (5/17–29.4%). One patient had grade III nausea and vomiting and one patient had grade III diarrhoea. Four patients had a WHO grade I rise in bilirubin during the first 4 weeks. The treatment-related mortality (TRM) was 1/17 (5.8%) attributable to Gram-negative (*Pseudomonas aeruginosa*) and Gram-positive (*Streptococcus*) septicæmia. The post mortem specified the cause of death as extensive bronchopneumonia.

Paraprotein response to ALL-IC

Fourteen patients had myeloma paraprotein in their blood at presentation, 12 were IgG and 2 IgA (10 kappa, three lambda and one was biclonal with kappa and lambda chains). The median paraprotein at diagnosis was 48 g/l (20–77 g/l). Prior to receiving ALL-IC, nine of these patients had complete disappearance of paraprotein from their blood and of the five patients who still had paraprotein present, two patients (Nos 11 and 16) had disappearance of paraprotein in their blood at 10 and 2 months post ALL-IC respectively.

Outcome post ALL-IC

Two of the nine patients who were in PR post HDM/PBSC achieved CR after ALL-IC. Six patients relapsed after ALL-IC and of these two are alive in PR after further therapy at 26 and 32 months from ALL-IC. Ten patients are alive in continuous CR/PR at a median of 35.5 months (19–112.5) after ALL-IC and 46 months (22–122.5) after the autograft. The actuarial OS of the entire group is 67% at 4 years from diagnosis and 63% at 3 years after ALL-IC.

Matched pair analysis for OS and EFS

Table 2 shows the details of the selection of the 34 matched controls in which it can be seen that the selection model has balanced the controls with ALL-IC patients for all variables. The OS and EFS curves (Figures 1 and 2) show no significant difference between the ALL-IC and matched controls. The median OS in the patients who received ALL-IC has not yet been reached (Figure 1). The OS has remained at above 50% for up to more than 10 years. At 3 years post ALL-IC, OS was 63% for the study group and 62% for the matched controls ($P = 0.89$). The EFS for ALL-IC was 48.3% vs 56.3% for matched controls at 3 years post ALL-IC ($P = 0.68$). Twelve of 17 patients on the ALL-IC arm remain alive. Six patients continue in CR post ALL-IC and four patients continue in stable PR.

Table 2 Comparison of variables at presentation between the study group ($n = 17$) and the matched controls ($n = 34$)

Variable	Study group		Matched controls		P value
	No.	Median	No.	Median	
Sex					
Male	13		24		0.66
Female	4		10		
Age		55 years		52 years	0.36
Diagnosis					
IgG	12		24		
IgA	2		4		1
BJ	2		4		
NS	1		2		
Chain					
K	11		24		
λ	4		8		1
K/ λ	1		0		
Blank	1		2		
Stage					
IA	2		1		
IIA	1		1		0.87
IIIA	12		30		
IIIB	2		2		
Ca		2.44		2.410	0.88
Urea		4.3		4.9	0.31
Creatinine		84		98.5	0.54
Albumin		37		35.5	0.56
Hb		11.1		10.5	0.75
WBC		6.0		6.3	0.52
Platelets		241		253.5	0.88
β_2 M		3.21		3.3	0.22
Pain grade					
0	11		15		
1	4		11		0.86
2	2		6		
3	0		2		
PS					
0	11		15		
1	6		12		0.82
2	0		4		
3	0		2		
4	0		1		
BL					
0	3		6		
1	1		1		1
2	1		2		
>2	12		25		

PS = performance status; BL = bone lesions.

Starting interferon

Out of 17 patients, five (29.4%) did not receive IFN after completing their high-dose therapy and went straight into ALL-IC. Of the 12 patients who received IFN pre-ALL-IC one developed bilateral femoral axonal neuropathy (No. 13) while on IFN and therefore was not started on IFN post ALL-IC and one died 15 days after ALL-IC. All the remaining 15 patients were able to start IFN maintenance post ALL-IC at a median of 2 (1–11 months). All the patients reattained their pre-ALL-IC dose of INF.

Discussion

As with acute leukaemia, complete remission in myeloma is an operational term which allows us to easily describe a

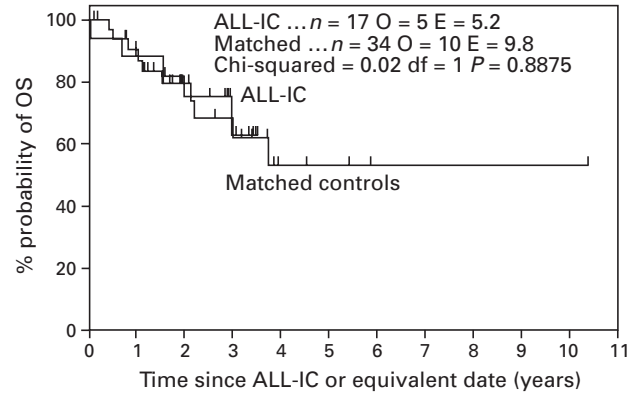


Figure 1 Log rank comparison of overall survival of patients (OS) who received intensive acute lymphoblastic leukemia consolidation chemotherapy (ALL-IC) ($n = 17$) vs the matched controls ($n = 34$).

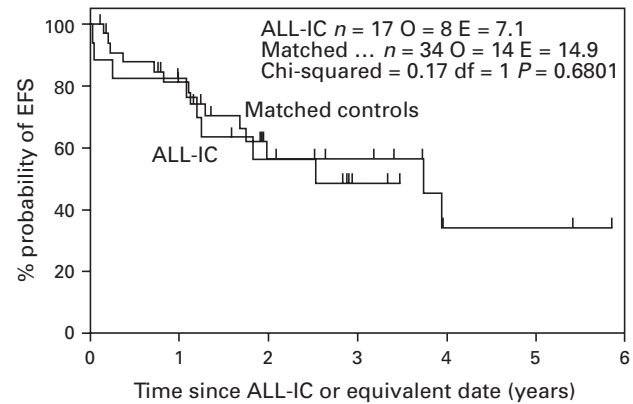


Figure 2 Log rank comparison of event-free survival (EFS) of patients who received intensive acute lymphoblastic leukemia consolidation chemotherapy (ALL-IC) ($n = 17$) vs the matched controls ($n = 34$).

clinical (and laboratory) endpoint which has a clear and highly significant correlation with outcome.^{3,26,27} However, this crude endpoint although extremely useful in determining new treatment methods for myeloma does not necessarily extrapolate into cure, and we know at a molecular level that there is still disease present. A few studies have reported achievement of molecular remissions following very intensive treatment in patients undergoing allogeneic bone marrow transplantation using immunoglobulin heavy chain (IgH) gene fingerprinting (a PCR-based technique), thus showing this is not an unattainable goal^{28,29} but for standard chemotherapy approaches the endpoint of molecular remission will be inappropriate because cure expectancy is very low.

Up until now intensive consolidation treatment for patients in CR or stable PR has always involved as the final event the putting back of stored remission marrow or PBSC which is potentially tainted with clonogenic myeloma cells. PCR-based studies have demonstrated that clonogenic tumour cells are detectable in the peripheral blood of almost all myeloma patients.^{30,31} CD38⁺ cells in myeloma may be clonogenic.³² There is evidence from studies on leukaemia^{33,34} and lymphoma³⁵ which suggests that residual tumour cells can contribute to relapse. Studies involving double transplants of necessity have a second autologous

rescue.⁸ The only trial so far reported of patients receiving any additional treatment after an autograft has involved the use of maintenance IFN⁶ and this biological agent is not producing cures in this setting.

The purpose of this present study was therefore to look at the use of intensive chemotherapy without autologous stem cell rescue, to be given after HDM/PBSC, as the last specific anti-myeloma treatment to be received by patients, thus avoiding the re-infusion of myeloma stem cells.

We selected the drugs used in this study with a view to targeting the biological nature of the myeloma stem cell in complete (or partial) remission. The hypothesis is that this stem cell originates from a post germinal centre B cell that has undergone immunoglobulin gene somatic hypermutation, VDJ recombination, antigen selection and isotype switch recombination,^{36,37} and that the clone involves the B cell lineage as far back as the pre-B cell.¹² It was with this background that this trial was designed to target the pre-B cells in patients who were in CR or stable PR after an autograft and possibly to aim for a long-term molecular remission.

We have therefore chosen the ALL-IC because it has been shown to be beneficial against pre-B stem cell disease when used as consolidation in both adult¹³ and childhood³⁸ ALL. In the MRC UKALL XA trial there was a significant reduction in the relapse risk post intensification.¹³

The fact that we were able to see two patients go into CR with the loss of paraprotein by immunofixation after ALL-IC is very encouraging but we have previously shown that the disappearance of paraprotein may take a long time after autografting³⁹ and the possibility that these patients had a delayed response to the high-dose therapy cannot be excluded. Thus, an effect if seen was at best moderate and could only be assessed for whether it could be clinically useful in the context of a formal trial. If useful it points the way to more extensive ALL strategies for treatment such as maintenance chemotherapy with 6-MP and methotrexate.

However, this study was about toxicity and we were obviously concerned that one of the 17 patients died of overwhelming Gram-negative and Gram-positive septicaemia. However, this is not significantly different from the treatment-related mortality of the use of ALL-IC in the MRC study in which six of 335 (1.8%) patients died as a consequence of the intensification block. This is in spite of our myeloma patients being significantly older; the median age for our myeloma group was 55 years and in the MRC study 69.4% of patients were under the age of 40 years.¹³ Our treatment-related death rate is also not significantly different from that seen with tandem autografting as published by Barlogie *et al*,⁸ in which 2/195 (1%) died during the first autograft and 3/151 (2%) died during the second autograft. The tolerance of the ALL-IC is also reflected in our overall survival analysis seen in Figure 1 in which patients were compared with the matched controls and in which we did not show that there was a negative impact upon survival as a consequence of patients receiving the ALL-IC. Twelve of the 17 patients remain alive and well with a median survival not yet reached.

Because of the inevitable delay after HDM/PBSC for recovery before ALL-IC can be given there is concern in

accounting for the median 6 month time lag between HDM/PBSC and ALL-IC when matched paired analysis is undertaken. The pair mates chosen for comparison were beyond 6 months post HDM/PBSC in all except one matched control who was 4 months post HDM/PBSC and matched for patient No. 11 (time period between autograft and ALL-IC was 1.5 months).

The morbidity of treatment in our patients relates almost entirely to neutropenia and is in keeping with the published data seen in ALL. Only 8/17 (47%) had grade 3–4 infection although all had grade 3–4 neutropenia, and this was in spite of our patients all having the typical marked immunoparesis of myeloma and half of them only being in partial remission.

An important analysis in this study was the assessment of the proportion of patients who could be recommenced or started on maintenance interferon post ALL-IC as it has been shown to be of benefit.⁶ We were therefore reassured to find that there was no compromise with the ALL-IC in being able to commence interferon in doses that were compared to controls.

Desikan *et al*,⁴⁰ in their study of 55 patients have shown that patients who received ≥ 2 cycles of DCEP as consolidation chemotherapy post tandem transplant, when compared to historical controls had a significantly higher EFS and OS ($P = 0.006/P = 0.01$). As our study was a phase I/II feasibility design it does not show the same degree of benefit due to small numbers, extreme variability in timing of consolidation and only one course of consolidation chemotherapy, but we have shown proof of principle in that post high-dose consolidation chemotherapy is feasible and well tolerated and in two patients there was disappearance of paraprotein which although not definitely indicating response nevertheless encourages further studies.

In conclusion, ALL-IC is therefore a relatively easily tolerated form of chemotherapy which can be given to CR and PR patients after an autologous transplant and should be the basis for the design of other randomised controlled trials of this form of chemotherapy given at this stage in the management of this disease.

It is fashionable at present to use biological methods for treating myeloma including dendritic cells⁴¹ and thalidomide,⁴² but our results from our randomised interferon trial were disappointing in that it appears no patients were cured. We feel it would therefore be a pity if there was not continued impetus to see if chemotherapy as given in pre-B leukaemia, with its known track record of cure, can be further assessed to maximise the best chance of determining whether some patients with this disease can be cured by these means. This could then be exploited further as was undertaken with leukaemia and of course would be part of a wide strategy for managing this disease including the use of biological agents.

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