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Patient perceptions of second transplants in myeloma: impact on recruitment in the British Society of Blood and Marrow Transplantation/UK Myeloma Forum Myeloma X Relapse (Intensive) Trial

The recruitment of patients with multiple myeloma (MM) in relapse to clinical studies, particularly of novel anti-myeloma agents, is generally straightforward, provided patients meet pre-specified clinical standards for fitness and evaluation of their disease. In contrast, patient attitudes to undergoing a second autologous stem cell transplant (ASCT) have had a considerable influence on recruitment to the British Society of Blood and Marrow Transplantation/UK Myeloma Forum (BSBMT/UKMF) Myeloma X Relapse (Intensive) Trial, which is now closed after showing superiority of the transplant over the non-transplant regimen (Cook *et al*, 2013).

The BSBMT/UKMF Myeloma X Relapse (Intensive) Trial was designed as a study of bortezomib-naive patients following relapse from induction therapy and first ASCT. Criteria for trial entry included duration of response of at least 18 months (reduced to 12 months in September 2011) and relapse requiring therapy (Cook *et al*, 2013). Age and fitness criteria were specified and the trial was limited to patients

Table I. Tick box summary of reasons for screened patients not entering the trial.

Reason	Number
Patient does not wish to participate	129 (25)
Patient too ill to consent	8 (2)
Patient clinically ineligible	197 (43)
Other reason	87 (3)
Not stated	7 (4)
Total	428

Numbers in parenthesis indicate patients with no additional information in free text.

Table II. Summary of reasons for non-registration using free text data.

Reason	Number
Clinically ineligible	198
No further details supplied	77
Participant choice	34
Did not want transplant	31
Did want transplant	18
Treating clinician decision	16
Wanted treatment locally	15
Not clinically fit for study	15
Refused	14
Miscellaneous	5
Preferred alternative study	3
Trial closed before registered	2
Total	428

Table III. Analysis of the main reasons of ineligibility for the trial.

Reason	Number
No previous transplant	39
Relapse ≤18 months	33
Patient on first treatment	25
Second relapse	15
Insufficient progression	14
No symptoms	9
On treatment	6
Relapse not confirmed on bone marrow	4
Previous allogeneic transplant	1

agreeing to full assessment of response in relation to measurable biochemical criteria. For those patients who were screened but not enrolled into the trial, the reason for non-trial entry was documented from a multiple-choice list. Investigators were encouraged to provide free text to expand on the reasons for non-entry. We have analysed the multiple-choice reasons and in particular, the free text entries to provide a more comprehensive picture of the reasons why patients could not or would not enter the trial.

In total, 725 patients were screened for the trial; 428 were not entered compared to the 297 patients who did enrol for participation in the trial. The reasons why patients were not entered were categorized and are shown in Table I. The additional data supplied by investigators showed a further and more comprehensive analysis of the reasons for non-entry (Table II).

Despite the clear trial protocol and eligibility criteria, a large number of patients were inappropriately staged and referred for inclusion. Tables III and IV show the main reasons of ineligibility and the number of patients whose clinical status did not match the trial criteria. In particular, when exploring the reasons why some patients excluded themselves from the trial, it was evident that quality of life and control may be an issue

Table IV. Significant co-morbidity and other reasons of ineligibility for the trial.

Reason	Number
Renal	14
Cardiac	5
Neuropathy	5
Hepatitis B	3
Neutropenia	3
Pulmonary	3
Thrombocytopenia	2
Hepatic	1
Mental	1
Second malignancy	4
Over the age limit	3
Previous bortezomib	3
Emergency radiotherapy	1
Previous allogeneic transplant	1
Latex intolerance	1
Other	2

for some potential participants, e.g. 15 patients did not want to undertake the travel to the centre performing the study and 31 patients did not want to have a second transplant. In contrast, 18 patients declined the study as they were quite determined that they wished to receive a second ASCT but were not prepared to defer this until after a second relapse.

Median survival at the first relapse after an ASCT for MM remains poor and it is clear that clinicians and patients are enthusiastic to find more effective treatment modalities than may be currently available. However, without an evidence-base to inform the patient consent decision, there was a clear expression of patient preferences and while 297 patients were recruited to the study, 64 patients (22%) excluded themselves on the grounds of a clear desire to avoid the inconvenience or trauma of an ASCT or, alternatively, to ensure they did receive an ASCT as their preferred therapy. We believe this analysis will help clinicians understand patient concerns about this important modality of treatment and that the results of BSBMT/UKMF Myeloma X Relapse (Intensive) Trial will help patients understand the benefits that may accrue from such intensive therapy.

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L-asparaginase with methotrexate and dexamethasone is an effective treatment combination in blastic plasmacytoid dendritic cell neoplasm

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare disease characterized by an aggressive clinical behaviour and a remarkably poor prognosis. It predominantly affects elderly males with an average age of 67 years at diagnosis and the affected organs are usually the skin, bone marrow, lymph nodes and central nervous system (Dalle *et al*, 2010). Most patients often respond to acute leukaemia–like chemotherapy, but relapses are almost inevitable, with median overall survival (OS) of 8–12 months in the largest patient series (Dalle *et al*, 2010; Pagano *et al*, 2013). Although BPDCN was classified as a myeloid malignancy in the 2008 World Health Organization classification, one recent retrospective study suggested that patients receiving an acute lymphoid leukaemia (ALL)/lymphoma-type regimen had a better response and better survival (Pagano *et al*, 2013). The importance of allogenic haematopoetic stem cell transplantation (allo-HSCT) to sustain remission was emphasized in both this and other trials (Pagano *et al*, 2013; Roos-Weil *et al*, 2013). Given that there is no consensus on the optimal therapeutic approach in this rare and aggressive disease, we chose to combine L-asparaginase with methotrexate, two synergistic drugs used in ALL treatment, insensitive to the multidrug resistance pathway and able to prevent central nervous system involvement.

Blastic plasmacytoid dendritic cell neoplasm was diagnosed in seven patients and confirmed by histopathology and flow cytometry using the criteria proposed by Garnache-Ottou *et al* (2009). These patients were treated in our institution with the AspaMetDex (L-asparaginase, methotrexate, dexamethasone) regimen between March 2006 and November 2012. All patients received three 21-d cycles of the (AspaMetDex) protocol, consisting of intravenous L-asparaginase (Kidrolase; EUSA Pharma, Oxford, UK) 6000 units/m^2 of body surface area on days 2, 4, 6, and 8, plus methotrexate 3 g/m^2 on day 1, and oral dexamethasone 40 mg from days 1–4. AspaMetDex regimen was continued until allo-HSCT or progression for responding patients. Patients who had allergic reactions to the L-asparaginase injections subsequently received Erwinia asparaginase (20 000 u/m^2, Erwiniase; EUSA Pharma) with the same schedule. Antithrombin and fibrinogen serum levels were measured before each injection of L-asparaginase. Patients with serum antithrombin levels below 60% of normal or fibrinogen levels under 0·5 g/l were given replacement therapy. All patients received alkaline hydration and leucovorin rescue with methotrexate, and anti-infectious prophylaxis with trimethoprim-sulfamethoxazole and valacyclovir. The primary endpoint was the response rate after three cycles assessed by clinical examination, bone marrow aspiration with flow cytometry and skin biopsy. Secondary endpoints were relapse-free survival (RFS), OS, and toxicity (Serious adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, Version 3, http://ctep.cancer.gov/protocolDevelopment electronic_applications/docs/ctcaev3.pdf).

The clinical and laboratory characteristics of patients are described in Table I. We analysed six males and one female, with a median age at diagnosis of 59 years (range, 54–73). All of them had skin and medullary involvement at diagnosis. One patient had been previously treated with six courses of CHOP (cyclophosphamide, doxorubicin, vincris-