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Phase II trial to investigate efficacy and safety of bendamustine, dexamethasone and thalidomide in relapsed or refractory multiple myeloma patients after treatment with lenalidomide and bortezomib

In the last decade several reports regarding the administration of bendamustine in relapsed/refractory multiple myeloma have been published in this journal (Ponisch *et al*, 2008; Ramasamy *et al*, 2011; Grey-Davies *et al*, 2012). The last one was the two-step phase II trial MUKone (Schey *et al*, 2015), which evaluated the deliverability and activity of two doses of bendamustine (60 mg/m^2 vs. 100 mg/m^2) days 1 and 8, thalidomide (100 mg) days 1–21 and low dose dexamethasone (20 mg) days 1, 8, 15 and 22 of a 28-day cycle. In 2013, based on these positive experiences, we designed a phase II trial (EudraCT #: 2011-001775-39) to determine the efficacy and feasibility of the combination of bendamustine, dexamethasone and thalidomide, as these had not been evaluated prospectively at that time. Treatment consisted of intravenously administered bendamustine at a dose of 60 mg/m^2 on days 1, 8 and 15, dexamethasone 20 mg per os on days 1, 8, 15 and 22 and thalidomide 100 mg daily per os on days 1–28 at an initial dose of 50 mg/day, with an increment to 100 mg after the first 15 days of treatment, repeated every 28 days for four to six cycles (BDT). Thrombosis prophylaxis was mandatory.

The primary objectives were to evaluate the efficacy of BDT in relapsed/refractory multiple myeloma patients after treatment with lenalidomide and bortezomib or who were ineligible to receive one or both of these drugs as measured by the rate of response in terms of overall response rate (ORR) and to assess the tolerability and toxicity. The secondary objectives were the evaluation of time to treatment failure (TTF), overall survival (OS) and, if possible, disease-free survival (DFS; time frame 18 months). Response during treatment was assessed after two and four cycles. Final response was assessed after the completion of the treatment. TTF, OS and DFS were estimated using Kaplan–Meier survival analysis. *P*-values were considered significant when $<0{\cdot}05$.

Given that patients included in the trial were heavily pretreated, an ORR, defined as the number of complete remissions (CR), very good partial remissions (VGPR) and partial responses (PR), of 25% was expected(Grey-Davies *et al*, 2012), whereas an ORR of 6% was considered as failure ($p0 = 0{\cdot}06$; $p1 = 0{\cdot}25$; alpha 0·032; power 90·2%; $N = 30$). The sample size was calculated with the one-sample multiple testing procedure according to Fleming (1982). The null hypothesis was considered to be refused if more than 5 of 30 patients did not respond to treatment.

A total of 30 patients were enrolled at 6 Italian cancer centres from July 2012 to September 2015. Four patients were excluded from the present analyses: two were screening failures, one patient died and another one left the country before treatment was started. As expected, most patients were heavily pre-treated with a median of 3·5 (range 1–7) treatment lines before BDT. Given that the inclusion criteria of the trial required refractoriness or ineligibility to bortezomib and lenalidomide, more than 88% of patients had received both drugs before BDT. Moreover, 58% of patients underwent autologous stem cell transplantation (SCT) before enrolment into the protocol and 4 patients received an allogeneic SCT. The median age at treatment start was 66 years (range 41–78 years). Clinical characteristics at time of enrolment are summarized in Table I.

Overall, 83 cycles of BDT were delivered, and patients underwent a median of three cycles (range 1–6). Eleven patients were able to complete four cycles and six underwent two more cycles (Fig 1A). Fifteen patients did not complete at least four treatment cycles, seven due to disease progression, four due to toxicity (two cases of grade 4 haematological toxicity, one deep vein thrombosis and one pulmonary embolism) and four for other non-treatment related causes (arteriopathy, pneumonia, worsening of pre-existing heart failure, cytomegalovirus infection). As expected, toxicity was not negligible and

Table I. Patient characteristics and previous treatments at time of enrolment, and maximum toxicity observed during the cycles of therapy ($n = 26$).

Variable	*n*	Total patients, *N*	Missing	%
Age, years		26	0	100
Mean	63			
Median	66			
Range	41–78			
Gender		26	0	
Male	10			38·5
Female	16			61·5
ISS stage		24	2	
I	12			50
II	4			16·7
III	8			33·3
Durie & Salmon stage		25	1	
I	5			20
II	4			16
III	16			64
Renal failure		25	1	
No renal failure	22			88
Renal failure	3			12
Bence-Jones proteinuria		26		
Yes	16			38·5
No	10			61·5
ECOG PS		25	1	
0	15			60
1	8			32
2	2			8
Lactate dehydrogenaase		24	2	
Normal	16			66·7
Elevated	8			33·3
Beta-2-microglobulin		23	3	
Normal	6			26·1
Elevated	17			73·9
Type of monoclonal component		26	0	
IgG kappa	8			30·8
IgG lambda	7			26·9
IgA kappa	4			15·4
IgA lambda	4			15·4
Lambda chains only	2			7·7
IgD lambda	1			3·8
Previous treatment lines		26	0	
Median	3·5			
Minimum	1			
Maximum	7			
Previous treatment types		26	0	
Thalidomide	10			38·5
Lenalidomide	24			92·3
Bortezomib	23			88·5
Polychemotherapy	4			15·6
Autologous stem cell transplantation		26	0	
0	11			42·3
1	9			34·6
2	5			19·2
3	1			3·8
Allogeneic stem cell transplantation	4	26	0	15·4

Adverse event	Grade 3 *n* (%)	Grade 4 *n* (%)	All grades *n* (%)
Anaemia	2 (8)	1 (4)	11 (42)
Leucopenia	0 (0)	1 (4)	4 (15)
Neutropenia	5 (19)	4 (15)	14 (54)
Thrombocytopenia	2 (8)	1 (4)	7 (27)
Fever	0 (4)	1 (4)	6 (23)
Infection	1 (4)	0 (0)	4 (15)
Febrile neutropenia	0 (0)	1 (4)	1 (4)
Cardiac general	0 (0)	0 (0)	0 (0)
Cardiac arrhythmia	0 (0)	0 (0)	3 (12)
Deep venous thrombosis	1 (4)	0 (0)	2 (8)
Pulmonary embolism	0 (0)	0 (0)	1 (4)
Gastrointestinal	0 (0)	0 (0)	4 (15)
Dermatology	0 (0)	0 (0	2) (8)
Neurology	0 (0)	0 (0)	1 (4)
Other*	3 (12)	0 (0)	8 (31)

ISS, International Staging system; ECOG PS, Eastern Cooperative Oncology Group performance status.

*Grade 3: Asthenia, pneumonia and poor clinical condition; Grade 2: two asthenia, one retinal tear and one pneumonia; Grade 1: two asthenia and one pneumonia.

adverse events were mainly haematological (Table I). Grade 3/4 anaemia occurred in three patients (12%), neutropenia in nine cases (35%) and thrombocytopenia in three (12%). Although patients received three doses of bendamustine 60 mg/m^2 at each cycle compared to two doses in the 60-mg arm (B60TD) of the MUKone trial (Schey *et al*, 2015), where patients in the 60-mg arm suffered ≥grade 3 anaemia (22%), ≥grade 3 neutropenia (33%) and ≥grade3 thrombocytopenia (31%), in the present study the haematological toxicity was similar to the MUKone trial. This suggests that higher doses of bendamustine can be delivered but must be subdivided into smaller single doses. Seven serious adverse events were reported: one each of pneumonia, deep vein thrombosis, pulmonary embolism, neutropenia, death due to sepsis, febrile neutropenia and diarrhoea.

In the present study, BDT was able to induce a VGPR in three patients (11%) and a PR in 7 patients (27%), leading to an ORR of 10 patients (37%) and so the null hypothesis was refused, confirming the efficacy of the investigated regimen. However, the ORR was slightly inferior than that reported in the MUKone trial (Schey *et al*, 2015) where 41·5% responded to B60TD. Of the remaining patients, three (11%) achieved stable disease and nine

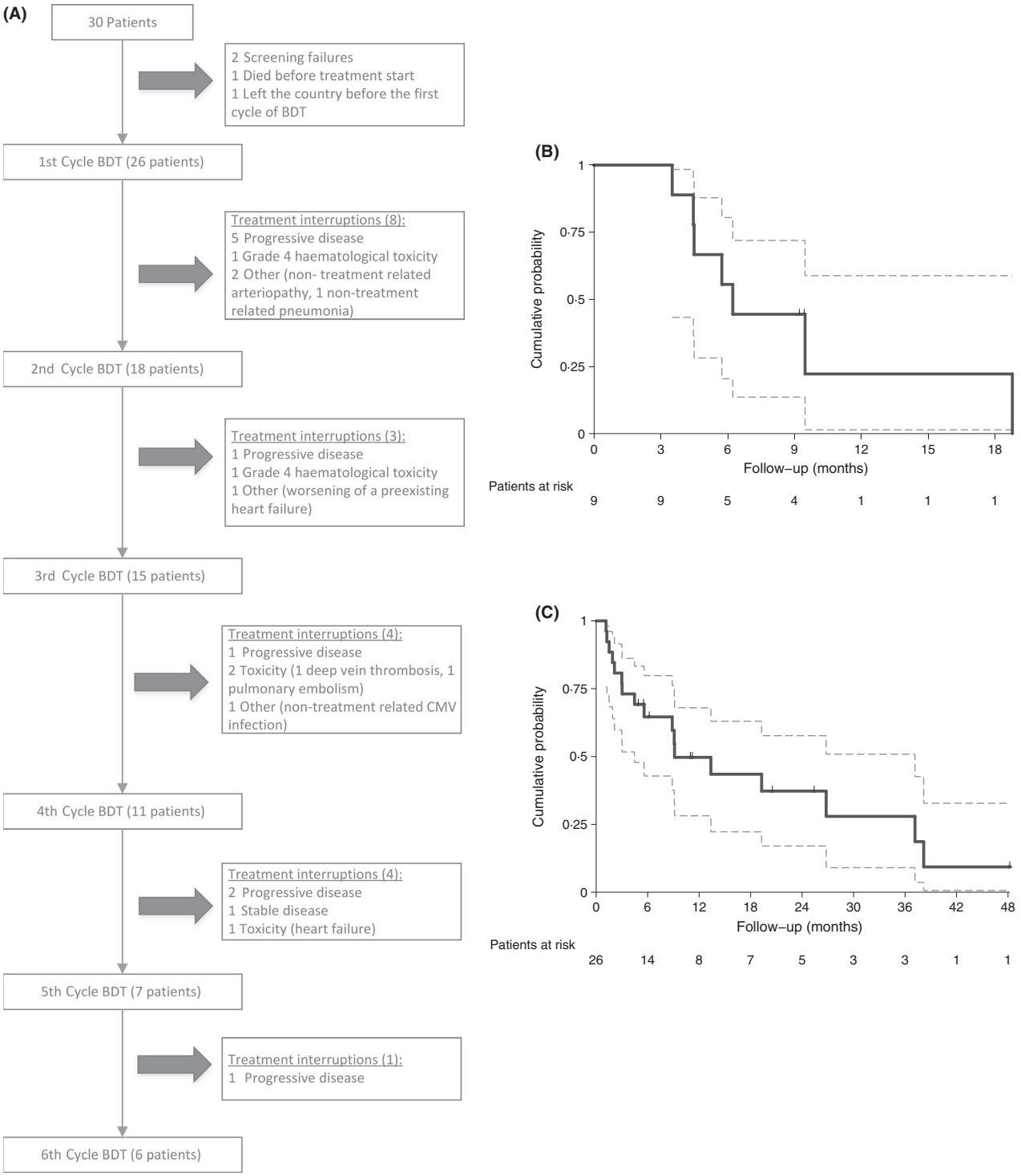

Fig 1. (A) Consort diagram. (B) Time to treatment failure and (C) overall survival. BDT, bendaustine, dexamethasone and thalidomide; CMV, cytomegalovirus.

(35%) progressed during treatment. During the observation period of 18 months after induction treatment, 10 more patients progressed, leading to an overall rate of progression of 73%. While DFS was not applicable because no patient achieved a CR, the TTF and OS at 18 months were 22% (median 6·2 months, range 3·5–18·7 months) and 40% (median 9·1 months), respectively (Fig 1B, C) compared to a 12-month OS and PFS of 45·3% and 6·5%, respectively, in the MUKone trial (Schey *et al*, 2015).

In conclusion, the combination of bendamustine, dexamethasone and thalidomide in a relapsed/refractory patient setting, is feasible and able to control the disease in this heavily pre-treated group of patients. However, this data has to be further evaluated in a phase III trial.

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Michael Mian: research design, acquisition of data, analysis and interpretation of data, wrote the paper. Norbert Pescosta: research design, acquisition of data, critical revision of the paper. Stefania Badiali: data management, analysis and interpretation of data, critical revision of the paper. Paola Cristina Cappelletto: research design, critical revision of the paper. Luigi Marcheselli: research design, analysis and interpretation of data, critical revision of the paper. Stefano Luminari: research design, critical revision of the paper, pharmacovigilance. Francesca Patriarca: acquisition of data, critical revision of the paper. Renato Zambello: acquisition of data, critical revision of the paper. Patrizia Mondello: acquisition of data, critical revision of the paper. Anna Pascarella: acquisition of data, critical revision of the paper. Giuseppe Tagariello: acquisition of data, critical revision of the paper. Alessandra Marabese: data management and acquisition of data, critical revision of the paper. Atto Billio: acquisition of data, critical revision of the paper. Sergio Cortelazzo: research design, acquisition of data, critical revision of the paper. All authors approved the submitted and final version.

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