STEPHEN BOYLE (Orcid ID : 0000-0002-3138-4815)

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Corresponding author mail id: boyle1986@gmail.com

Significance statement

Our study highlights that for patients with myeloma treated with the chemotherapy drug bortezomib, the number of cycles of treatment received is an important predictor of survival. Our conclusions from a restrospective look at patients treated in Australia and New Zealand in the recent past were slightly different from those of another group who have recently published their findings in this journal which we explore further in this letter to the editor

Receiving four or fewer cycles of therapy predicts poor survival in newly diagnosed transplant ineligible patients with myeloma who are treated with bortezomib-based induction

Authors and affiliations:

Stephen Boyle[1], Cameron Wellard[2], Elizabeth M. Moore[2], Hilary Blacklock[3], SJ Harrison[4], P. Joy Ho[5], Jay Hocking[6], Zoe K. McQuilten[2], Hang Quach[7], Ruth Spearing[8], Erica M. Wood[2], Andrew Spencer[9], Peter Mollee[1] on behalf of the Myeloma and Related Diseases Registry Investigators.

1 - Princess Alexandra Hospital & The University of Queensland, Brisbane, Australia

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2 - School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
3 - Middlemore Hospital, Auckland, New Zealand
4 - Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Sir Peter MacCallum Dept of Oncology, University of Melbourne
5 - Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia
6 - Box Hill Hospital, Melbourne, Victoria, Australia
7 - University of Melbourne, St. Vincent's Hospital, Victoria, Australia
8 - Christchurch Hospital, Christchurch, New Zealand
9 - The Alfred Hospital, Monash University and Australian Centre for Blood Diseases, Melbourne, Victoria, Australia

We read with interest the study from Rampotas et al (1) where they evaluated 158 transplant-non-eligible newly diagnosed myeloma patients treated with bortezomib (Velcade), cyclophosphamide and dexamethasone (VCD) chemotherapy. They showed that fixed duration VCD led to an overall response rate (ORR) of 72% and was 'reasonably well tolerated'. They concluded that the comparatively poor event free survival (EFS) may be improved "with the use of higher cumulative bortezomib" doses.

Other studies have reported survival benefit with higher cumulative dose of bortezomib administered, both in the clinical trial setting (2) and in 'real world' cohorts (3, 4). Many elderly and frail patients, however, cannot tolerate standard bortezomib-based regimens and consequently cease treatment prematurely, which may be the main factor underlying poor survival. If this is the case, alternate dosing strategies may be the key to improving outcomes.

We evaluated 289 newly diagnosed non-transplant eligible myeloma patients diagnosed between 22/07/2011 and 19/01/2018 and treated with bortezomib-based chemotherapy from the Australian and New Zealand Myeloma and Related Diseases Registry (5, 6), Table 1. The impact of baseline characteristics, response and number of cycles of bortezomib on overall survival was assessed in a 12-month landmark analysis using Cox regression analysis. 32% of patients received 4 or fewer cycles of treatment. In a multivariate landmark analysis, worse overall survival was predicted by more advanced ISS stage (HR 3.05 [95%CI 1.35-6.89] for ISS II vs I; HR 3.1 [95% CI 1.34-7.17] for ISS III vs I), thrombocytopenia (HR 0.99 [95%CI, 0.99-1.00]), and receiving 4 or fewer cycles of therapy (5-8

cycles vs 1-4 cycles = HR 0.45 [95%CI 0.24-0.82]; ≥9 cycles vs 1-4 cycles = HR 0.57, [95%CI 0.34-0.98], Figure 1). Patients who received 4 or fewer cycles (Table 1) had a trend toward older age and worse ECOG performance status but did not have worse disease by ISS stage or high-risk FISH. Cessation due to toxicity or death occurred in 53% of those receiving 4 or fewer cycles versus 28% of those receiving 5-8 cycles and only 5% of those receiving ≥9 cycles ($p<0.01$). The main specific toxicities that led to treatment cessation in all groups were: neuropathy (n = 29, 10%), GI side effects (n=6, 2%), infections (n=6, 2%), malaise (n=5, 2%) and cytopenias (n=3, 1%), consistent with the known side-effect profile of bortezomib.

In summary, in our landmark analysis, receiving 4 or fewer cycles of bortezomib-based therapy was an independent predictor of inferior overall survival in patients with newly diagnosed non-transplant eligible myeloma. Receiving 4 or fewer cycles was not associated with worse disease but with early cessation due to toxicity with patients being older and having worse performance status. As opposed to the conclusion of Rampotas et al, our findings suggest that improved outcomes will come from devising regimens with improved tolerability rather than maximising the cumulative dose of bortezomib. It may be that, in the case of bortezomib, these are essentially the same idea: ongoing low intensity bortezomib may allow patients to stay on therapy, develop deeper more durable responses, maximise their cumulative bortezomib exposure and potentially improve survival. Prospective studies assessing frailty-adapted dosing strategies are required in elderly myeloma patients treated with bortezomib to improve the chance of adequate therapy delivery.

Tables and figures:

Figure 1: OS by number of cycles of bortezomib chemotherapy received, 1-year landmark analysis

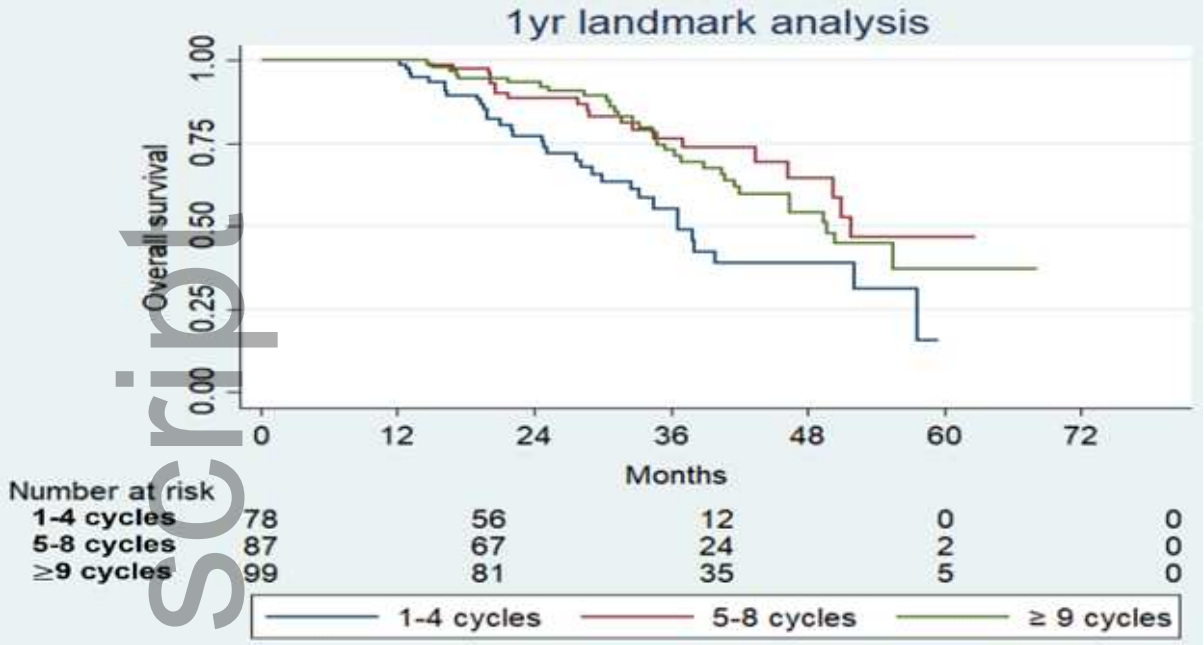

Table 1: Baseline characteristics and outcomes

	All patients	Received ≤4 cycles	Received 5-8 cycles	Received ≥9 cycles
N	289	93	95	99
Median age (range)	74yrs (47-92)	75yrs (55-92)	74yrs (55-92)	73yrs (47-92)
Age group:				
≤70yrs	29%	28%	26%	31%
70-75yrs	33%	28%	32%	38%
75-80yrs	21%	18%	26%	18%
>80yrs	17%	26%	16%	12%
Female gender	41%	44%	40%	38%

Median creatinine	94 umol/L	103 umol/L	95 umol/L	93 umol/L
ISS:				
Stage I	20%	20%	15%	25%
Stage II	44%	48%	43%	43%
Stage III	35%	32%	42%	32%
ECOG Performance Status:				
0, 1	74%	66%	72%	82%
2, 3 or 4	26%	34%	28%	18%
High risk FISH:	19%	9%	25%	22%
Chemotherapy regimen:				
VCD	85%	85%	86%	84%
MPV	4%	6%	4%	4%
Vd	6%	8%	2%	6%
Other	5%	1%	8%	6%
Bortezomib dose:				
1.3mg/m2	67%	60%	83%	58%
1.5mg/m2	29%	38%	15%	35%
Subcutaneous	91%	92%	93%	90%
Reason for bortezomib cessation:				
Completed planned therapy	60%	30%	64%	94%
Toxicity or early death	28%	53%	28%	5%
Suboptimal response or progression	7%	14%	7%	1%
Response:				
CR	17%	8%	16%	25%
VGPR	32%	28%	30%	37%
PR	36%	37%	39%	33%
Non-responder	15%	27%	15%	4%
Median PFS	24 months	21 months	24 months	24 months
Median OS	46 months	33 months	51 months	50 months

*VCD: Bortezomib, Cyclophosphamide and Dexamethasone; MPV: Melphalan, Prednisolone and Bortezomib; Vd: Bortezomib and Dexamethasone

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