Ann Hematol (2010) 89:1019–1027
DOI 10.1007/s00277-010-0959-4

ORIGINAL ARTICLE

A staged approach with vincristine, adriamycin, and dexamethasone followed by bortezomib, thalidomide, and dexamethasone before autologous hematopoietic stem cell transplantation in the treatment of newly diagnosed multiple myeloma

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Received: 13 July 2009 / Accepted: 6 April 2010 / Published online: 29 April 2010

Abstract Bortezomib-based regimens have significant activities in multiple myeloma (MM). In this study, we tested the efficacy of a total therapy with a staged approach where newly diagnosed MM patients received vincristine/adriamycin/dexamethsone (VAD). VAD-sensitive patients (≥75% paraprotein reduction) received autologous hematopoietic stem cell transplantation (auto-HSCT), whereas less VAD-sensitive patients (<75% paraprotein reduction) received bortezomib/thalidomide/dexamethasone (VTD) for further cytoreduction prior to auto-HSCT. On an intention-to-treat analysis, a progressive increase of complete remission (CR) rates was observed, with cumulative CR rates of 48% after HSCT. Seven patients progressed leading to three fatalities, of which two had central nervous system disease. The 3-year overall survival and event-free survival were 75.1% and 48.3%, respectively. Six patients developed oligoclonal reconstitution with new paraproteins. In the absence of anticoagulant prophylaxis, no patients developed deep vein thrombosis. The staged application of VAD+/–VTD/auto-HSCT resulted in an appreciable response rate and promising survivals. Our approach reduced the use of bortezomib without compromising the ultimate CR rate and is of financial significance for less affluent communities.

Keywords Staged approach · VAD · VTD · Survival · Oligoclonal reconstitution · CNS disease

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Introduction

Multiple myeloma (MM) has a low possibility of cure. However, important therapeutic improvements have been made. Scheduled autologous hematopoietic stem cell transplantation (auto-HSCT) after initial cytoreduction has resulted in a complete remission/near-complete remission (CR/nCR) rate of about 20% [1], which translates into a benefit in overall survival (OS). Recently, the advent of targeted therapy such as bortezomib results in important advances in the treatment of MM. Bortezomib, a proteasome inhibitor that inhibits nuclear factor kappa B [2], leads to a CR/nCR rate of 10% in heavily treated, refractory, and relapsing patients with MM [3, 4].

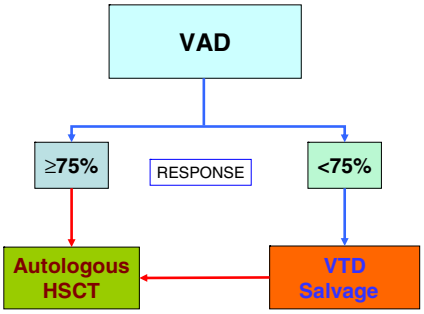

Fig. 1 Algorithm of patient treatment

Moreover, upfront use of bortezomib in combination with chemotherapy has resulted in a CR rate about of 20% (17–43%) even in the absence of auto-HSCT [5, 6]. This is an important aspect in the management of MM as MM is a disease of the elderly, with the majority of the patients ineligible for auto-HSCT that leads to a high CR rate [1]. Furthermore, bortezomib is non-myelotoxic and hence may be used in combination with conventional chemotherapy. Indeed, synergism of tumor cytotoxicity has been demonstrated when chemotherapy is combined with bortezomib, thus restoring chemosensitivity to previously chemoresistant tumor cells [7, 8]. Based on these encouraging data, the upfront use of bortezomib in combination with conventional chemotherapy has been tested in younger patients before HSCT and in elderly patients who are not HSCT candidates. Expectedly, the upfront use of combined bortezomib and chemotherapy has resulted in a CR rate of about 20–30% in elderly patients [9] and a more encouraging CR rate of about 50% in younger patients when followed by auto-HSCT [10, 11]. The improved CR rates have translated into superior progression-free survival and OS [12].

Both bortezomib and HSCT have emerged as important components in the management of MM, although their roles and timing relative to each other have not been determined. Bortezomib is an expensive medication with significant side effects. To optimally position bortezomib and HSCT, we reasoned that patients reaching a satisfactory response with conventional treatment might not need additional cytoreduction with bortezomib pre-HSCT. However, for patients with suboptimal response to conventional treatment, additional cytoreduction with bortezomib pre-HSCT might improve the outcome. Therefore, a staged approach was adopted in which newly diagnosed myeloma patients who achieved a ≥75% reduction in paraprotein level after standard vincristine, adriamycin, and dexamethasone (VAD) would proceed to auto-HSCT, whereas those with a <75% paraprotein reduction would receive bortezomib, thalidomide, and dexamethasone (VTD) for additional cytoreduction prior to auto-HSCT.

Table 1 Patient demographics (N=25)

Median age (years, range)	54 years (33–65)
Male/female	17/8
Paraprotein	
IgG	12 (48%)
IgA	4 (16%)
IgD	2 (8%)
Light chain	7 (28%)
Durie–Salmon stage	
IA	2 (8%)
IIA	4 (16%)
IIIA	13 (52%)
IIIB	6 (24%)
International staging system	
I	7 (28%)
II	7 (28%)
III	11 (44%)
DAPK methylation (N=21)	4 (19%)
Median β_2M (μg/mL, range) Normal: <1.42 μg/mL	4.67 μg/mL (1.92–13.2 μg/mL)
Median serum albumin (g/L, range) Normal: 42–54 g/L	30 g/L (17–49 g/L)
Median CD34 positive cell dose/kg body weight	5.56×10^6 (range: 2.88–20.4×10^6)
Median days to neutrophil engraftment	18 (10–29)

Ig immunoglobulin

International staging system [13]

Durie-Salmon staging system [14]

Table 2 Cumulative response after each stage of treatment

	Post-VAD (*N*=25)	Post-VTD (*N*=25)	3-month post-Auto-HSCT[a] (*N*=25)	3-month post-Auto-HSCT (*N*=21)
CR	1 (4%)	2 (8%)	12 (48%)	12 (57.1%)
nCR	3 (12%)	4 (16%)	1 (4%)	1 (4.8%)
VGPR	4 (16%)	8 (32%)	5 (20%)	3 (14.3%)
PR75	3 (12%)	9 (36%)	5 (20%)	5 (23.8%)
PR50	5 (20%)	0	0	0
MR	6 (24%)	0	0	0
NR	3 (12%)	2 (8%)	2 (8%)	0

VAD vincristine, adriamycin, dexamethsone, *VTD* velcade, thalidomide, dexamethasone, *HSCT* hematopoietic stem cell transplantation, *CR* complete response, *nCR* near-complete response, *VGPR* very good partial response, *PR75* partial response with 75–90% paraprotein reduction, *MR* minor response, *NR* no response, *PR50* partial response with 50–75% paraprotein reduction

[a] Intention-to-treat analysis

Materials ad methods

Patients, treatment algorithm, and protocol The study started in October 2005. The median follow-up time was 17 months (range, 7–39 months). Inclusion criteria were newly diagnosed MM with symptoms, age <65 years, measurable disease, serum creatinine <3 times the upper reference value (normal, 82–126 μmol/L), and adequate liver function [15]. All patients received initial cytoreduction with three cycles of VAD. Those achieving ≥75% reduction in paraprotein proceeded to HSC mobilization with cyclophosphamide (4 g/m^2 intravenously) and granulocyte colony stimulating factor (300 μg/day subcutaneously unit leukocyte recovery). Patients with <75% reduction in paraprotein received VTD (bortezomib, 1.3 mg m^{-2}day^{-1} intravenously on days 1, 4, 8, and 11; thalidomide, 200 mg/day; and dexamethasone, 40 mg/d orally from days 1–4 and days 8–11). Thalidomide and bortezomib dosage was reduced to 75% for World Health Organization grade III toxicity and omitted for grade IV toxicity. Fourteen of the 25 patients proceeded to VTD salvage therapy because of <75% reduction in paraprotein level. Of these 14 patients, all received four cycles of VTD, except one who had only three cycles of VTD due to grade IV neurotoxicity. Auto-HSCT conditioning regimen comprised intravenous melphalan at 200 mg/m^2. Four patients did not receive auto-HSCT. Two patients opted for allogeneic HSCT with HLA-identical siblings, and they were censored after completion of VTD. The other two patients had primary refractory disease or rapidly progressive disease during VTD therapy. All patients received thalidomide (100–200 mg/day) as maintenance therapy regardless of whether VTD had been used. Prophylactic cotrimoxazole for *Pneumocystis jirovecii* was routinely prescribed. The protocol was approved by the institution review board in accordance with the Declaration of Helsinski, and informed consent was obtained from all participating patients. The treatment algorithm was shown in Fig. 1. Toxicity was reported after initial VAD and after VTD according to the Common Terminology Criteria for adverse events v3.0.

Staging and laboratory investigations MM workup included bone marrow examination, skeletal survey, serum β_2-

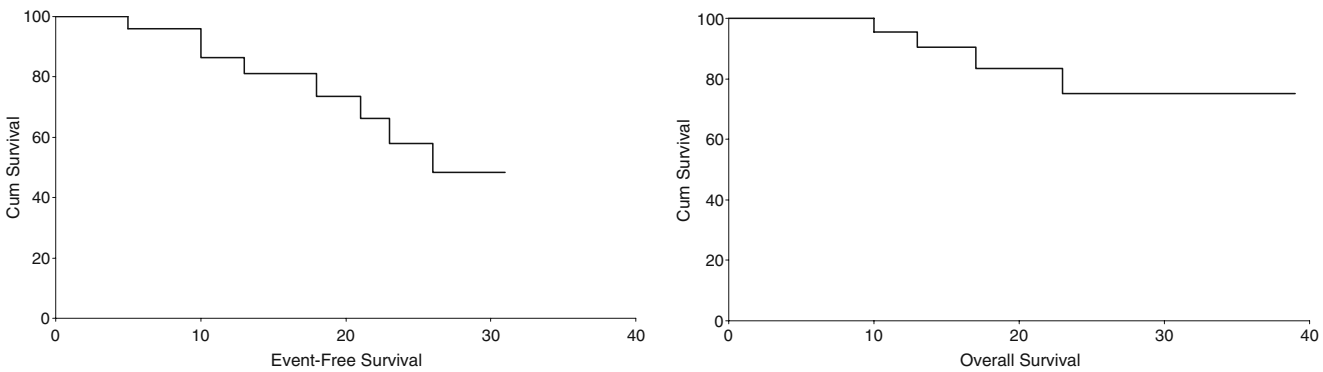

Fig. 2 Overall survival and event-free survival of 25 patients

Table 3 Side effects after VAD and VTD

After VAD	VAD (*N*=25)	VTD (*N*=14)
Grade 3/4 myelotoxicity	10 (40%)	0
Sensory neuropathy (grade 2)	12 (48%)	12 (85.7%)
Tremor	2 (8%)	4 (28.6%)
Grade 1	2	3
Grade 3	0	1
Proximal muscle weakness	2 (8%)	4 (28.6%)
Grade 2	1 (4%)	2
Grade 3	1 (4%)	2
Mucositis (grade 2)	2 (8%)	0
Gastrointestinal	3 (12%)	7 (50%)
Constipation	2 (8%)	7
Grade 1	2	5
Grade 2	0	2
Epigastric pain	1 (4%)	0
Deep vein thrombosis	0	0
Infection/febrile episode	7 (28%)	4 (28.6%)
Fever	2	0
Hickman line infection	2	0
HSV sacral ulcer	1	0
Pneumonia/bronchitis	1	1
CMV hepatitis	1	0
Zoster	0	1
Folliculitis	0	1
Enterobactor	0	1
Steroid-induced diabetes mellitus	1 (4%)	1 (7%)

CMV cytomegalovirus, *HSV* herpes simplex virus

microglobulin (β_2M) level, serum protein electrophoresis (SPE), urine protein electrophoresis, serum or urine immunofixation, paraprotein level assay, and serum free light chain (FLC) assay (Freelite, The Binding Site, Birmingham, UK) [16]. All sera were assessed with SPE and FLC immunoassays. Urine was assessed for monoclonal FLC by immunofixation.

Response criteria All patients were analyzed on an intention-to-treat basis. Bone marrow plasmacytosis and paraprotein levels were assessed prior to treatment, after VAD, after VTD, and 3 and 6 months after auto-HSCT. Responses were defined according to standard criteria [17]. CR was defined as complete resolution of disease with absent paraprotein, as evidenced by a negative SPE and immunofixation, and <5% plasma cells in the bone marrow. nCR was defined as a negative SPE but positive immunofixation. Partial response (PR) was sub-classified into very good partial remission (VGPR, paraprotein reduction ≥90%), PR75 (paraprotein ≥75% but <90% reduction), and PR50 (paraprotein ≥50% but <75% reduction). Minor response (MR) was defined as paraprotein reduction of ≥25% but <50%. No response (NR) was defined as paraprotein reduction of <25%. Progression was defined as ≥25% paraprotein increase in two consecutive tests 4 weeks apart. Relapse was defined as reappearance of the paraprotein on immunofixation in CR patients, positive SPE in the nCR patients, and/or appearance of new bone lesions. For patients with light-chain MM (LCMM), CR was defined as normalization of the level and ratio of serum FLC and negative serum and urine immunofixation. Oligoclonal reconstitution was defined as the appearance of a new paraprotein not present at diagnosis, which persisted for ≥4 weeks. Six of the patients developed a paraprotein different from that at diagnosis during CR or plateau phase and, hence, a "clonal change". However, the origin of the new clone was not clear and might imply development of a second malignancy entirely unrelated to the original disease. Therefore,

Table 4 Oligoclonal reconstitution in six myeloma patients

Case	Original paraprotein	New paraprotein	Paraprotein level	Time of onset of new paraprotein	remark	Outcome
C1	κ	IgGκ	WQ	CR	Same light chain	Persisted for 11 months
C2	λ	IgGλ	WQ	CR	Same light chain	Persisted × 4 months
C3	IgAκ	IgGκ		CR	Different heavy chain	Persisted × 13 months
C4	IgDλ	IgGκ	8 g/L	CR	Different paraprotein	Persisted × 5 months
C5	IgGκ	double IgGκ	2.1 g/L	PR75	Additional clone	Persisted × 5 months
C6	κ	IgGκ	1.7 g/L	CR	A complete immunoglobulin with the same light chain	Persisted × 1 month

WQ too weak to quantitate, *CR* complete remission, *PR75* partial response with 75% reduction in paraprotein

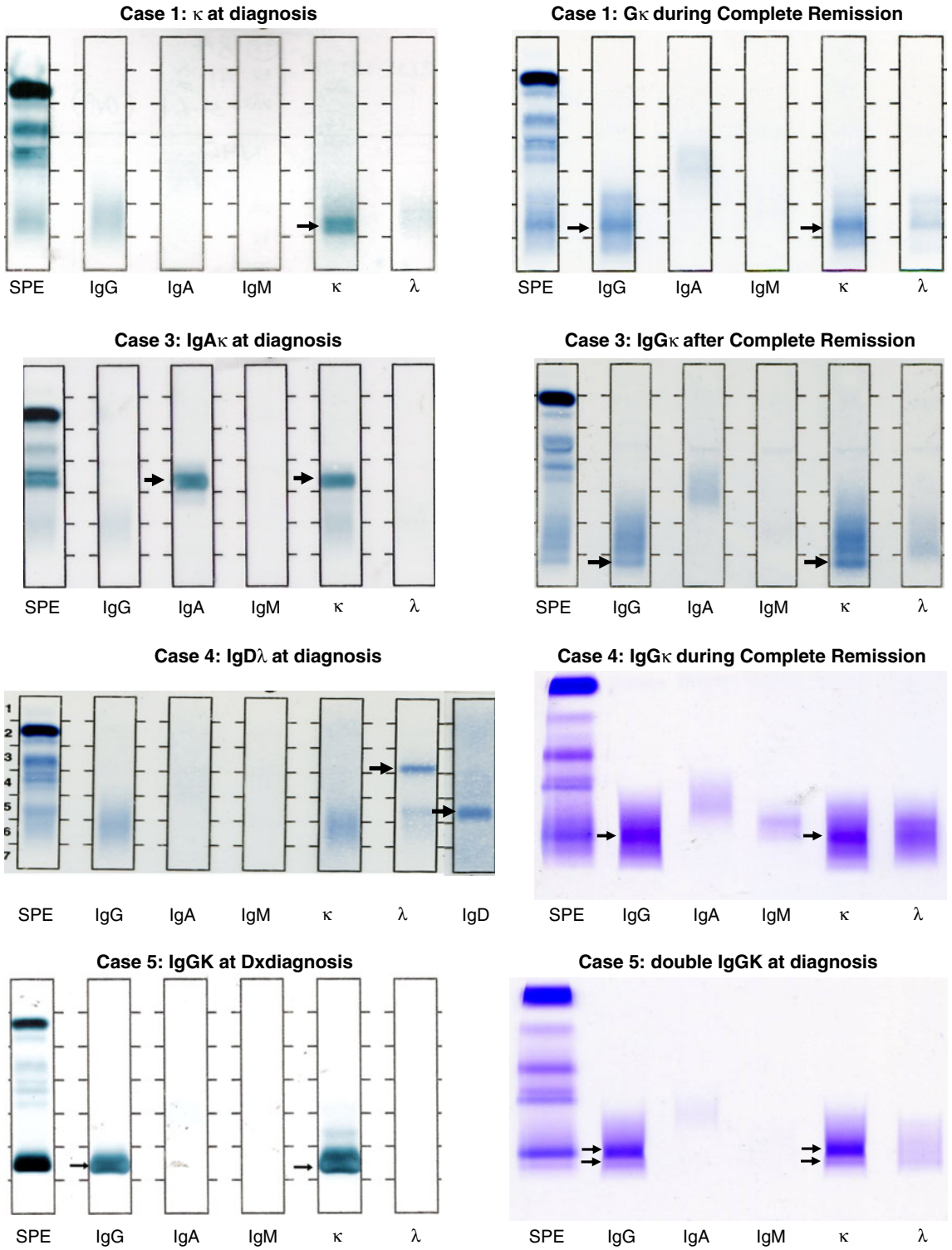

Fig. 3 Oligoclonal reconstitution in MM patients. *Upper left* showed clonal change of free kappa at diagnosis to IgGκ during complete remission (*CR*). *Upper right* showed clonal change from IgAκ at diagnosis to IgGκ during CR. *Lower left* showed clonal change from IgDλ (*arrows*) plus free λ (*arrowhead*) at diagnosis to IgGκ during CR. *Lower right* showed clonal change from single IgGκ at diagnosis to double IgGκ during CR

Table 5 Characteristics and outcome of the seven patients with disease progression

Patient	Paraprotein	DS stage	ISS stage at Diagnosis	Best response	Time from treatment to progression (months)	Survival after progression (months)	Outcome	Site of progression
P1	Light chain	IIIA	III	CR	10	3	Death	BM + skin plasmacytoma + circulating plasma cell
P2	IgG	IIIA	II	CR	26	10+	Alive with disease	BM
P3	IgG	IIIA	II	PR75	13	4	death	CNS + BM
P4	IgA	IIIA	III	CR	18	5	death	Extramedullary + BM
P5	IgG	IIIB	III	Progressive disease	5	8+	Alive with disease	Pleural
P6	IgG	IIIA	II	CR	21	14	Alive with disease	BM
P7	IgG	IIIA	II	VGPR	23	16	Alive with disease	BM

Ig immunoglobulin, *CR* complete response, *PR75* partial response with 75–90% paraprotein reduction, *VGPR* very good partial response, *BM* bone marrow, *CNS* central nervous system

in the case of oligoclonal reconstitution, the absence of the original paraprotein by serum/urine immunofixation still qualified for CR.

Statistical analysis The primary endpoint was response rate. Secondary endpoints were survivals. OS was defined as time from commencement of induction therapy to death or last follow-up. Event-free survival (EFS) was defined as time from commencement of induction therapy to the date of progression, relapse, or death. Survival curves were plotted by Kaplan–Meier method.

Results

Patients The demographics of the patients were shown in Table 1. There was an incremental upgrade of response after each stage of treatment (Table 2). After VAD, 14 (56%) proceeded to receive VTD. The CR rate was 4% after VAD, 8% after VTD, and 48% in an intention-to-treat analysis after HSCT, or 57% for patients who actually completed HSCT. All patients undergoing auto-HSCT had at least PR75 pre-HSCT. The projected 3-year OS was 75.1% (Fig. 2). Seven patients progressed, all having DS stage III disease with ISS stage II in four and stage III in three cases. The 3-year EFS was 48.3% (median, 26 months; Fig. 2). Four patients died (all with DS stage IIIA disease), one of primary refractory disease, two of relapses after prior CR, and one of progression from PR.

Side effects (Table 3)

After VAD, 12 (48%) patients developed grade 2 sensory neurotoxicity, two (8%) tremor (one grade 1, one grade 2), three (12%) with GI side effects (two grade 1 constipation, one epigastric pain), and seven (28%) infective/febrile episodes. After VTD, 11 (78.6%) had sensory neuropathy (grade 3, $N=4$; grade 4, $N=1$). Of these 11 VTD patients with sensory neuropathy, seven already had grade 2 sensory neuropathy after VAD, of which three had static grade 2 sensory neuropathy and four had increased severity of neuropathy (neuropathy increased from grade 2 to 3, $N=3$, and grade 2 to 4, $N=1$). Another four patients with no neuropathy after VAD developed neuropathy after VTD (grade 2, $N=3$; grade 3, $N=1$).

Oligoclonal reconstitution Six patients developed oligoclonal reconstitution, five after CR (as defined by disappearance of the initial paraprotein; Table 4). Three patterns were observed. Cases 1, 2, and 6 with initially LCMM developed a complete immunoglobulin paraprotein. Case 5 developed an additional paraprotein with the same immunoglobulin subtype. Finally, cases 3 and 4 developed an entirely different paraprotein. For patients with a measurable new paraprotein, the level appeared to be stable over a period of 1–11 months (median, 5 months; Fig. 3).

CNS relapse Patient P4 (Table 5) with stage IIIA IgA MM achieved PR50 after VAD and CR with VTD. Acute spinal

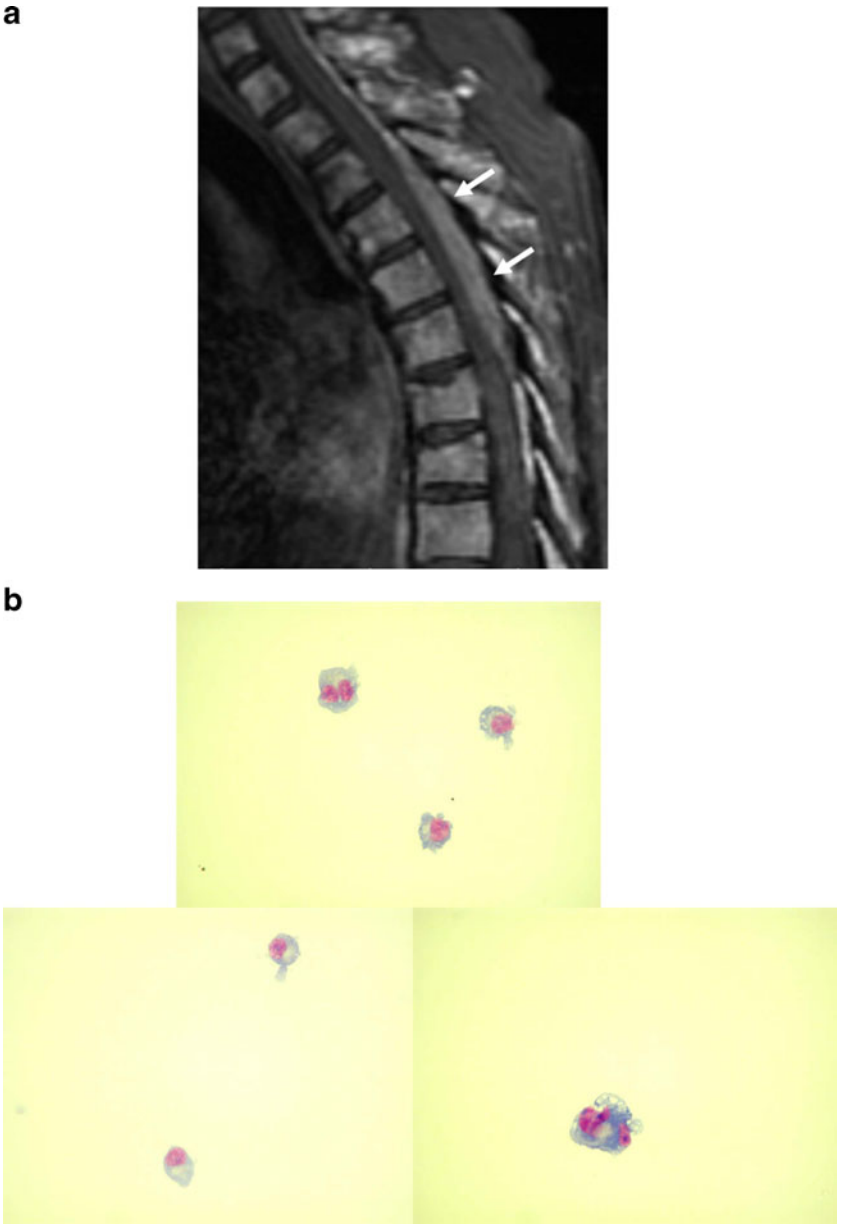

Fig. 4 **a** Sagittal fat-saturated SE T1W scan obtained after administration of intravenous gadolinium contrast agent showing an enhancing epidural mass (*arrows*) in the posterior spinal canal compressing the thoracic cord. **b** Cerebrospinal fluid showed myeloma cells

cord compression developed a year after HSCT, with IgA increasing to 2,020 mg/dL (normal <386 mg/dL). Magnetic resonance imaging showed an extensive thoracolumbar extradural mass with cord compression (Fig. 4a). He achieved a partial response after bortezomib-CMP (cyclophosphamide, melphalan, and prednisolone) [8], but died of disease progression 2 months afterwards. Patient 3 with DS IIIA MM achieved PR75 after VAD, which was maintained with thalidomide after HSCT. Sudden diplopia due to right abducens nerve palsy and skin nodules developed 7 months after HSCT. Computerized axial tomography did not reveal any abnormality. The cerebrospinal fluid showed elevated protein 1.36 g/L (normal < 0.6 g/L) and a cell count of 52×10^6/L with 96% plasma cells (Fig. 4b). The serum paraprotein level resurged to 27 g/L. Bone marrow examination showed 28% pleomorphic plasma cells. He refused further treatment and died 4 weeks afterwards.

Discussion

In this study, the response to standard VAD was used to dichotomized patients to a chemosensitive group (≥75% paraprotein reduction after VAD) who proceeded directly to auto-HSCT and a relative chemoresistant group (<75%

paraprotein reduction) who received additional cytoreduction with VTD before auto-HSCT. We surmised that this staged approach might maximize the reduction of neoplastic cells prior to HSC mobilization and restrict the use of the expensive bortezomib to chemoresistant patients.

There are several interesting observations. We achieved a cumulative CR rate of >50% after auto-HSCT. Recent studies showed that first-line use of bortezomib-based regimens gave CR rate of up to 30% even without HSCT [9]. Furthermore, total therapy using bortezomib-containing regimens for initial cytoreduction prior to auto-HSCT resulted in a CR rate of about 50% (43% to 56%) [10–12]. Therefore, the results in this study provide an alternative method of achieving an appreciable CR rate with a reduced use of bortezomib. In less affluent countries or health care systems, our approach offers a means of alleviating the financial burden of bortezomib without compromising the overall treatment results of patients with MM.

Despite the relatively high CR rate after auto-HSCT in our cohort, it is noteworthy that the CR rate only changed from 4% to 8% when VTD was used in patients not responding optimally to VAD. These results contrasted that of the regimen (PAD, bortezomib, doxorubicin, dexamethasone) in untreated MM patients where the CR rate was around 25% after PAD alone [10, 11]. While these results could not be directly compared as different regimens were used on dissimilar patient populations, this disparity might be partially explained by the fact that only relatively chemoresistant patients received VTD in our study.

On the other hand, using VAD upfront resulted in very frequent (48%) sensory neuropathy prior to VTD. Moreover, eight had new onset or increased severity of neuropathy after VTD. Therefore, it would have been more preferable to use AD instead of VAD to avoid excessive neuropathy without compromising the chemotherapy response prior to VTD.

On follow-up, a significant number of patients developed a new paraprotein distinct from the one at diagnosis. Indeed, development of isotypic change and oligoclonal bands has been reported in about 10% of MM patients undergoing HSCT [18]. The long-term outcome of these new clones remains to be determined. If these new clones represented expansion of minor subclones consequent to effective elimination of major clones, this phenomenon of oligoclonal reconstitution might become more common as more effective treatment becomes available. Alternatively, appearance of the new clone might represent clonal evolution from the original clone. Case 5 who developed two Gκ bands evolving from one Gκ at diagnosis might be explained by this mechanism. Whatever the pathogenesis, oligoclonal reconstitution affects the management of patients. Firstly, the diagnosis of CR may be difficult. In our case, we define CR as the absence of the original clone, and hence, the emergence of another clone does not alter the diagnosis of CR. Secondly, the long-term outcome of these new clones in our patients is yet to be defined, which might be transient [18].

Two of our patients developed central nervous system (CNS) myeloma at progression in addition to cutaneous deposition and plasma cell leukemia. This is a rare complication [19, 20], and the factors predisposing to CNS dissemination remain to be elucidated. However, it would have been ideal if clonal analysis of the CSF plasma cells had been performed.

Finally, deep vein thrombosis (DVT) did not occur in any of our patients despite the omission of prophylaxis. In Western patients, when thalidomide was combined with dexamethasone or chemotherapy, the risk of DVT might be increased to 10–27% [21]. Our observation concurred with another study showing a low incidence of DVT in a cohort of 85 Chinese MM patients receiving thalidomide [22]. Moreover, the incidence of DVT in Chinese has been shown to be much less frequent than Caucasian patients to the extent that prophylaxis is not a standard practice even in patients undergoing orthopedic surgery [23, 24]. This disparity might at least be partially explained by the absence of factor V Leiden and prothrombin 20210 mutations, both hereditary thrombophilic tendencies prevalent in Caucasians, in the Chinese population [25, 26]. Therefore, we believe that Chinese patients do not require prophylactic aspirin while receiving thalidomide.

In conclusion, our VAD-VTD/auto-HSCT algorithm resulted in a high response rate and promising survivals. This staged approach has significant financial implications in the treatment of MM.

Acknowledgement We thank Drs Joyce Chan, Bonnie Khoo, Herman Liu, Thomas Lau from Pamela Youde Nethersole East Hospital; Drs Dominic Yeung, M.F. Law, Candia Chan and L.G. Wong from Tuen Mun Hospital; Drs K.K. Lee, Joycelyn Sim, Vivien Mak and Sandy Ho from Princess Margaret Hospital, for their patient referral and management. We also thank Mr Edwin Leong for funding support of bortezomib.

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