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An open label phase I/II study of cyclophosphamide, bortezomib, pegylated liposomal doxorubicin and dexamethasone in newly diagnosed myeloma

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Abstract

We conducted a phase 1/2 trial evaluating the combination of cyclophosphamide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone (CVDD) for newly diagnosed multiple myeloma (MM). The primary objective of the phase 1 was to evaluate the safety and tolerability of maximum planned dose (MPD) and the phase 2 was to assess the overall response rate. Patients received 6–8 cycles of CVDD at 4 dose levels. There were no dose-limiting toxicities. The MPD was cyclophosphamide 750 mg/m² IV on day 1, bortezomib 1.3 mg/m² IV on days 1, 4, 8, 11, pegylated liposomal doxorubicin 30 mg/m² IV on day 4, and dexamethasone 20 mg orally on the day of and after bortezomib (21-day cycle). Forty nine patients were treated at the MPD of which 22% had high-risk myeloma. The most common grade 3 toxicities included myelosuppression, infection and fatigue. Overall response and complete response rates were 91% and 26% in standard-risk, and 100% and 58% in high-risk cohort, respectively. After a median follow-up of 34 months, the median progression-free survival was 31.3 months. The 2-year overall survival was

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Author Contribution:

R.B., K.S., D.S., and M.A. conceived and designed the research.

T.N., R.B., K.S., J.L.O.B., D.S., and M.A. provided study material and patients, and preformed research.

T.N. and M.A. collected data.

T.N., J.K., B.Y., and M.A. analyzed and interpreted the data.

J.K. and B.Y. performed statistical analyses.

T.N. and M.A. wrote the manuscript.

T.N., R.B., K.S., J.K., J.L.O.B., B.Y., D.S., W.D., and M.A. approved the final manuscript.

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91.1% in the standard-risk and 88.9% in the high-risk cohort, respectively. CVDD regimen was well tolerated and was highly active in newly diagnosed MM.

Keywords

Multiple myeloma; bortezomib; pegylated liposomal doxorubicin; cyclophosphamide

Introduction

Multiple myeloma is an incurable B-cell hematologic malignancy characterized by the preferential proliferation of plasma cells in the bone marrow (1, 2). The landscape of myeloma treatment has drastically changed recently as multi-agent combination systemic therapy which incorporates novel agents such as bortezomib and lenalidomide has produced significant responses (3–8). Combination of bortezomib (Velcade®), pegylated liposomal doxorubicin (Doxil®) and dexamethasone (VDD regimen) has demonstrated significant anti-myeloma activity in relapsed/refractory setting (9–11), as well as in newly diagnosed multiple myeloma patients for which phase 2 trials of VDD demonstrated an overall response rate (ORR) of 85 to 86% and a very good partial response (VGPR) plus complete response (CR) rate of 28 to 53% (12, 13).

Despite major advances achieved in the treatment of multiple myeloma, the management of patients with high-risk myeloma remains a challenge, due in part to the inability to induce durable responses (5, 14–16). High-risk myeloma is mainly defined by the presence of hypodiploidy, deletion of 17p, t(4;14), t(14;16) by fluorescence *in situ* hybridization (FISH) and deletion 13q by conventional cytogenetics, consensus recommendations set forth by the panel of international myeloma experts (17). Current practice is to consider bortezomib-based regimens in these patients given the data from several trials showing that bortezomib may be able to overcome the poor prognosis features rendered by these genetic abnormalities, particularly t(4;14), which is characterized by overexpression of fibroblast growth factor receptor 3 (FGFR3) and drug resistance (14, 18, 19). Additionally, achievement of a CR has been shown to be important in establishing durable responses particularly in high-risk myeloma (20).

Synergistic activity between bortezomib and alkylating agents including melphalan and cyclophosphamide has been demonstrated both in pre-clinical models and in patients by many investigators (18, 21–24). Given the established synergism we hypothesized that incorporating an alkylator to VDD regimen, specifically CVDD (cyclophosphamide, bortezomib (Velcade®), pegylated liposomal doxorubicin (Doxil®) and dexamethasone) may increase the depth of response and may improve the long term outcome of newly diagnosed both standard-risk and high-risk multiple myeloma patients. Here we present the results of a prospective phase 1/2 study of the CVDD regimen in patients with newly diagnosed multiple myeloma from a single institution.

Methods

Patient population

Eligible patients were older than 18 years of age, had newly diagnosed multiple myeloma requiring systemic therapy based on the International Myeloma Foundation diagnostic criteria (25). An Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 (ECOG performance status of 3 was allowed if related to myeloma bone disease), and a left ventricular ejection fraction of 50% or greater by multigated acquisition scan or a 2-D echocardiography were required. Patients needed to have measurable myeloma paraprotein levels in serum (< 0.5 g/dL) or urine (< 0.2 g excreted in a 24-hour urine collection sample), or serum involved free light chains (> 10 mg/dL) provided that the kappa/lambda ratio is abnormal. Other eligibility criteria included the following: $<$ grade 2 peripheral sensory neuropathy, absolute neutrophil count (ANC) < 1000 cells/mm³, hemoglobin level < 8.0 g/dL, platelet count $< 100,000$ cells/mm³, serum creatinine level > 2.5 mg/dL, aspartate/alanine aminotransferase > 2.5 times the upper limit of normal, total bilirubin level > 1.5 times the upper limit of normal, and absence of other significant comorbidities (for example, myocardial infarction within 6 months of enrollment, uncontrolled pulmonary disease or ongoing severe infection). Those with a bone marrow containing $> 50\%$ plasma cells were permitted to have a platelet count $< 100,000$ cells/mm³. High-risk myeloma was defined by the presence of at least one of the following characteristics: deletion of chromosome 13 by conventional cytogenetics; hypodiploidy; t(4;14) by FISH; t(14;16) by FISH; deletion of 17p by FISH based on the consensus recommendations (17).

This clinical trial was conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonization for Good Clinical Practice. The study was approved by the Institutional Review Board of the University of South Florida. All study participants provided voluntary written informed consent. The trial was registered at www.clinicaltrials.gov as NCT00750815.

Study Design

The primary endpoints of the study were to determine the maximum tolerated dose (MTD) of cyclophosphamide when given in combination with bortezomib at different doses at 1.0 or 1.3 mg/m², pegylated liposomal doxorubicin and dexamethasone (CVDD) and to evaluate the overall response (CP+VGPR+ partial response (PR)) rate for patients with newly diagnosed active multiple myeloma. Secondary endpoints were to evaluate progression-free survival (PFS), disease-free survival (DFS) and overall survival (OS) after CVDD. Patients were treated with inter-patient escalating doses of cyclophosphamide (250 mg/m² for dose level 1, 500 mg/m² for dose level 2, and 750 mg/m² for dose levels 3 and 4) on day 1 of each 21-day cycle; bortezomib at escalating doses (1.0 mg/m² for dose levels 1 through 3, and 1.3 mg/m² at dose level 4) on days 1, 4, 8, and 11; pegylated liposomal doxorubicin 30 mg/m² on day 4; and oral dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 (Table Ia). Patients defined as having high-risk myeloma and who had responsive disease (CR, VGPR, or PR) received 2 additional cycles (a total of 8 cycles), and proceeded to autologous hematopoietic cell transplantation (HCT) after achieving maximal response from CVDD regimen (in their first responses) or at the time of early relapse at the discretion of treating

physician. Those patients defined as having standard-risk myeloma received 6 to 8 cycles of therapy and received autologous HCT at the discretion of treating physician.

All patients received acyclovir or an equivalent antiviral therapy for herpes zoster prevention. For deep venous thrombosis (DVT) prophylaxis they received aspirin (81 or 325 mg daily), low-molecular weight heparin, or full anticoagulation with warfarin at the discretion of treating physician as the VDD study reported an increased risk of thromboembolic events in initial 10 patients with later successful prophylaxis with protocol modification requiring either aspirin or low molecular weight heparin (12). Thromboprophylaxis was held when a platelet count fell below 50,000 cells/mm³. After one patient expired due to pneumonia, the study protocol was amended to mandate bacterial prophylaxis with levofloxacin 500 mg daily or ciprofloxacin 500 mg twice a day, and fungal prophylaxis with fluconazole 400 mg daily. All antibiotics were continued throughout the protocol treatment. Antibiotics were substituted with alternative agents if required at the discretion of treating physician. Use of an intravenous (IV) bisphosphonate was recommended. The use of granulocyte-colony stimulating factor (G-CSF) was not permitted to render a patient eligible for the study. In the Phase 1 component of the study, the use of G-CSF was not permitted during cycle 1 of therapy, but was allowed beyond cycle 1 or once the assessment of dose-limiting toxicity (DLT) was completed. During the Phase 2 of the study, the use of G-CSF was allowed in all cycles.

Dose escalation and phase 2 dose determination

There were a total of 4 dose levels planned to determine the MTD of the CVDD regimen (Table Ia). In the phase 1 portion of the trial, the first cohort of three subjects was enrolled to dose level 1. A full safety evaluation was conducted when these subjects had completed one cycle (21 days) of CVDD. After the safety data for each dose level were evaluated, the subsequent cohort was enrolled.

DLTs were defined as: grade 3 non-hematologic toxicity attributed to one or more of the study drugs; grade 4 hematologic toxicity (including a platelet count < 10,000 cells/mm³ on more than one occasion despite transfusion support; grade 4 neutropenia (ANC < 500 cells/mm³) occurring for more than 5 days and/or resulting in neutropenic fever with elevated temperature (defined as 101 °F) confirmed on two occasions; or the inability to receive the day 1 dose for cycle 2 due to continued drug-related toxicity from cycle 1 or drug-related toxicity newly encountered on day 1 of cycle 2. Lymphopenia, a recognized side effect of either bortezomib or dexamethasone, was not considered a DLT. Dose modifications were not allowed during cycle 1 of the phase 1 portion of the study unless a patient experienced a DLT.

Assessments

Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Patients were evaluable for safety assessment if they received at least one dose of study treatment, and were evaluable for efficacy assessment if they received at least one cycle of study treatment. Patients were assessed for treatment response based on International Myeloma Working Group (IMWG) uniform criteria (26).

Statistical analysis

The dose escalation in the phase 1 portion followed the standard 3+3 design with 4 possible dose levels. The Kaplan-Meier method was used to estimate PFS (time from the initiation of therapy to progression/relapse or death from any causes, which were censored at date last known progression/relapse-free and alive), DFS (time from initiation of therapy to first documentation of disease progression/relapse or death), and OS (time from initiation of therapy until death from any cause) (27). Response rates were reported with both a point estimate as well as a Clopper-Pearson 95% confidence interval (CI). Expecting at least 90% of ORR with the protocol regimen, an improvement over an ORR of 78% or lower with standard of care, a sample size of 80 for the phase 2 portion of the study was planned to test the one-sided hypothesis with 90% power and 4.5% type I error rate. The trial was closed early after a total of 58 patients were enrolled due to slow accrual and shortage of pegylated liposomal doxorubicin (28). The data cutoff was December 31st, 2012; analyses were performed using SAS version 9.3.

Results

Patient characteristics

A total of 58 patients were enrolled in this phase 1/2 study from September 2008 to August 2011: 12 in phase 1 and 46 in phase 2 (Table Ia). Three patients were treated at dose level 4 (the maximal planned dose (MPD)) during the phase 1. Baseline patient and disease characteristics are listed in Table Ib. The median age was 57 (range, 25 – 77) years, and 34 (59%) patients were males. The median β 2-microglobulin level was 3.55 mg/L (range, 1.16 – 11.3). Forty nine patients were treated with MPD (3 patients in phase 1 portion) and were included in the statistical analyses for the responses and survival endpoints. Cytogenetics and/or FISH results for risk stratification were available in 54 (93%) subjects, of which 12 patients (22%) had high-risk disease.

Determination of MTD/MPD

No DLTs were observed in the phase 1 portion of the study and doses were safely escalated to dose level 4. The MPD was reached at dose level 4 (cyclophosphamide 750 mg/m², bortezomib 1.3 mg/m², pegylated liposomal doxorubicin 30 mg/m², and dexamethasone 20 mg) without toxicity and this dosing was selected for the phase 2 component of the study (Table Ia).

Treatment and safety

The median number of cycles completed by patients is 6 in the standard-risk cohort and 8 in the high-risk cohort, respectively. The proportion of patients who were able to complete all of the prescribed therapy (either 6 or 8 cycles) was 81% in the standard-risk cohort and 75% in the high-risk cohort, respectively. At least one level of dose reduction was required in 34 of 58 patients (59%). Dose reductions for bortezomib, pegylated liposomal doxorubicin, cyclophosphamide, and dexamethasone were required in 45%, 29%, 7%, and 10% of patients, respectively. The most common reasons for dose reduction for each agent were the following: for bortezomib, neuropathy (including autonomic neuropathy) (56%) and fatigue

(9%); for pegylated liposomal doxorubicin, hand-foot syndrome (46%) and neutropenia (8%); for cyclophosphamide, neutropenia (50%); and for dexamethasone, fluid retention (50%).

Grades 3 toxicities occurring during the phase 1 portion of the study (beyond DLT observation period) were rash (hand-foot skin reaction) 16.7%, hypophosphatemia 16.7%, thrombocytopenia 8.3%, and hypocalcemia 8.3%. Grade 4 toxicities occurring during the phase 1 portion of the study was neutropenia (8.3%). Grades 3–4 toxicities for patients treated at MPD were summarized in Table II. The most common grades 3–4 toxicities included myelosuppression, infection, and fatigue (Table II). One patient died of bilateral pneumonia after cycle #5 of CVDD therapy at MPD dosing (grade 5 toxicity). Grade 3 and 4 peripheral neuropathy were seen in 8% and 4%, respectively. As expected, grade 2 neuropathy was seen in 39% and grade 2 hand-foot syndrome was seen in 12% of patients at MPD dosing.

Response

Table III summarizes the best response rates without transplants in 58 patients stratified by the risk group. The ORR at best response after CVDD chemotherapy (without transplant) was 91.3% (95% CI: 79.2% - 97.6%) in the standard-risk cohort and 100% (95% CI: 73.5% - 100%) in the high-risk cohort, respectively. The rates of VGPR were 88.3% in the high-risk cohort and 63% in the standard-risk cohort, respectively. The rate of CR (including stringent CR) was higher in the high-risk cohort compared to the standard-risk cohort at 58.3% and 28.3%, respectively. Response rates after cycle 4, 6, and 8 of therapy for all patients versus patients treated with MPD dosing are shown in Figure 1a and 1b, respectively. With 39 responders out of 42 evaluable patients after at least 4 cycles of MPD dosing, the study had one-sided p-value of 0.01 for the primary endpoint evaluating the ORR.

Stem cell mobilization and collection

Thirty nine patients (67%) received HCT (including 2 syngeneic and 3 allogeneic) after the treatment with CVDD regimen. All 34 patients who attempted autologous stem cell collections were successful. The stem cell mobilization and collection were performed following the institutional guidelines. G-CSF was used alone in 29 patients and in combination with plerixafor in 5 patients. On an unplanned analysis, the median numbers of CD34⁺ cells collected were 5.62 (range, 2.76 – 13.12) $\times 10^6$ /kg for G-CSF alone (n=29) and 4.22 (range, 2.29 – 5.18) $\times 10^6$ /kg for G-CSF and plerixafor. The percentages of patients collected in one day were 69% for G-CSF alone and 80% for G-CSF plus plerixafor, respectively.

Outcomes

Thirty patients are alive and without disease progression the time of analysis. One patient died as a result of infection which was considered treatment-related mortality, and 25 patients have progressed at the time of manuscript preparation. With a median follow up of 33.8 (range, 4.2 – 50.9) months, the median PFS is 31.3 months (95% CI: 24.5 – not reached) (Figure 2a). There was no difference in PFS based on risk stratification (P=0.39)

but as an exploratory analysis 3-year PFS does differ by transplant status (56.3% in transplant groups vs. 15.7% in no transplant group, $P=0.015$). The median OS has not been reached (Figure 2b). The 2-year OS is 91.1% in the standard-risk cohort and 88.9% in the high-risk cohort, respectively ($P=0.39$). The OS stratified by transplant status did not differ (data not shown).

Discussion

The results of this phase 1/2 study to evaluate CVDD regimen as an induction therapy for newly diagnosed multiple myeloma patients show that CVDD is highly active with an ORR of 93%, a VGPR or better rate of 67%, and a CR rate of 35%. Approximately 80% of standard-risk and 75% of high-risk patients, respectively, were able to complete prescribed therapy. The regimen was relatively well tolerated, with manageable side effects even though grade 3 or 4 hematologic toxicities occurred in up to 22 % of patients. The most common grade 3 or 4 non-hematologic toxicities were fatigue (10.2 %), and infection (10%). Neutropenia can be managed with G-CSF support and dose reductions of either bortezomib or liposomal doxorubicin. Though the protocol allowed serum creatinine up to 2.5 mg/dL, most of our study participants had normal serum creatinine with a median of 1.1 mg/dL. The feasibility of this regimen in myeloma patients with renal failure is uncertain. Stem cell mobilization and collection was successful in all patients who attempted a standard mobilization method. One of the limitations of the study was overall younger patient population compared to the usual median age of myeloma diagnosis. Durie-Salmon staging was either 2 or 3 in more than 90% of patients but ISS staging was relatively lower with only half of patients were in stage II or III at the time of enrollment. The proportion of patients who completed prescribed therapy (either 6 or 8 cycles) was lower in patients equal to or older than 60 years of age (91% in the group with ages < 60 vs. 63% in the group with ages ≥ 60) and we recommend careful monitoring and judicious dose reduction in those patients equal to or older than 60 years of age exhibiting early toxicities.

A similar combination regimen termed ABCD (liposomal doxorubicin, bortezomib, cyclophosphamide and dexamethasone) has been evaluated by an Italian group as salvage therapy for patients with relapsed/refractory myeloma (29). ABCD regimen resulted in 50% clinical response including 29% with VGPR or better. This study is the first report of this combination regimen for newly diagnosed myeloma. The addition of cyclophosphamide to the already established VDD regimen resulted in a similar overall response rate, but a higher VGPR or better rate. Though the dose of cyclophosphamide can be increased up to 1000 mg/m² intravenously every 3 weeks in a combination regimen of cyclophosphamide, bortezomib and dexamethasone (i.e., CyBorD) (30), we used 750 mg/m² of cyclophosphamide in CVDD regimen due to the addition of liposomal doxorubicin (i.e., quadruple regimen). Although comparisons across various phase 2 studies will need to be performed cautiously, multiple other combination regimens have shown similar response rates and PFS estimates at 2 years as summarized in Table IV. Patients with high-risk myeloma defined by cytogenetic abnormalities remain a significant treatment challenge as they continue to have inferior PFS and OS. We evaluated the efficacy of this regimen in patients with high-risk disease compared to patients with standard-risk. Based on prior reports suggesting that bortezomib may overcome the poor prognosis seen in these patients,

high-risk patients in this study received 8 cycles of the CVDD regimen. While the number of high-risk myeloma patients was small and our study enrolled a less than a targeted number of patients in the phase 2 portion, the CVDD regimen resulted in higher CR rate (58.3%) in high-risk cohort than in standard-risk cohort (28.3%). Caution is advised when interpreting the results of PFS and/or OS as majority (i.e., 67%) of patients received HCT for consolidation therapy and the imbalance in age. Most current myeloma induction regimens contain a proteasome inhibitor (e.g., bortezomib) and/or an immunomodulatory agent (e.g., lenalidomide). Recent efforts have focused on simultaneous targeting of multiple pathways and upfront use of promising novel agents, hence the number of agents combined are increasing with the short-term goal to achieve deeper responses. Attainment of a CR has been correlated with improved progression-free and overall survival in some studies (20, 31). The commonly employed research strategy is to combine 3 or 4 active agents to aim for deeper responses in myeloma patients in order to produce longer remission and ideally survival benefit while minimizing the toxicity. However, even with the most contemporary combination regimens with impressive overall response rate, a fraction of patients continue to suffer from refractory multiple myeloma. Selected phase 1 and 2 prospective studies of induction regimens utilizing novel agents for patients with newly diagnosed multiple myeloma are summarized in Table IV. In the published two randomized phase 2 trials comparing triplet and quadruple regimens, the addition of fourth agent did not result in improved outcomes as response rates were similar with triplet regimens and quadruplets appear to cause increased toxicities (32, 33). It is conceivable that investigators may preferentially target high-risk myeloma population with more intensive therapy, however, the value of quadruplet regimens in patients with high-risk multiple myeloma remains to be determined. It is also imperative that induction therapy does not compromise our ability to collect stem cells for transplant eligible patients.

Before any of the quadruplet regimens are accepted as standard of care, larger prospective clinical trials are required to validate the impressive responses seen in many of the combination regimens utilizing 3 or 4 agents due to the lack of superiority in efficacy and increased toxicities. The landscape of myeloma upfront therapy continues to evolve with the addition or more promising newer agents including carfilzomib and pomalidomide (34–36).

Conclusions

The four-drug combination regimen of CVDD produces high quality responses and is reasonably well tolerated with judicious dose reductions and adjustments in newly diagnosed multiple myeloma patients, irrespective of their cytogenetic risk status. Stem cell mobilization and collection can be safely and successfully performed in all patients after CVDD induction therapy. The high rate of CR and longer OS in high-risk patients warrant further evaluation of the CVDD regimen in this patient population.

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Key Points

CVDD regimen produces high response rates, is well tolerated and highly active in patients with newly diagnosed multiple myeloma.

Figure 1a.

Figure 1b.

Figure 1.

Figure 1a. Response rates after CVDD chemotherapy (All patients)*

Abbreviations: CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

*Responses are after defined cycles of CVDD chemotherapy (without high-dose therapy)

Figure 1b. Response rates after CVDD chemotherapy (MPD dosing)*

Abbreviations: CR, complete response; MPD, maximal planned dose; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

*Responses are after defined cycles of CVDD chemotherapy (without high-dose therapy)

Figure 2a.

Figure 2b.

Figure 2.
Figure 2a. Progression-free survival (PFS)

Figure 2b. Overall survival (OS)

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Table 1a

Patient disposition by dose level in the phase 1 and phase 2 components

Dose level	Cyclophosphamide dose, mg/m ²	Bortezomib dose, mg/m ²	Pegylated liposomal doxorubicin dose, mg/m ²	Dexamethasone dose, mg	No. of patients enrolled
Phase 1: Dose escalation (n=12)					
1	250	1.0	30	20	3
2	500	1.0	30	20	3
3	750	1.0	30	20	3
4	750	1.3	30	20	3
Phase 2: After MTD determination (n=46)					
4	750	1.3	30	20	46

Abbreviations: MTD, maximum tolerated dose; No., number

Table 1b

Baseline patient and disease characteristics

Characteristic	All patients (n=58)	Patients treated at MPD (n=49)
Median age, year (range)	57 (25–77)	57 (25–75)
Male gender, n (%)	34 (59)	26 (53)
Race, n (%)		
White	48 (83)	39 (80)
Black	8 (14)	8 (16)
Other	2 (3)	2 (4)
MM subtype, n (%)		
IgG	31 (53)	26 (53)
IgA	14 (24)	11 (23)
IgD	1 (2)	1 (2)
κ light chain	8 (14)	7 (14)
λ light chain	4 (7)	4 (8)
ISS stage II/III, n (%)	31 (53)	26 (53)
Durie-Salmon stage II/III, n (%)	53 (91)	44 (90)
β2-microglobulin (mg/L), median (range)	3.55 (1.16 – 11.3)	3.4 (1.6 – 11.3)
Serum creatinine (mg/dL), median (range)	1.1 (0.5 – 3.7)*	1.1 (0.5 – 3.7)*
Serum albumin (g/dL), median (range)	3.9 (1.9–4.7)	3.8 (2.3 – 4.7)
Cytogenetics/FISH, n (%)		
Deletion 13q by cytogenetics	2 (3)	2 (4)
Deletion 17p by FISH	6 (10)	6 (12)
t(4;14) by FISH	4 (7)	5 (10)
High-risk (based on cytogenetics/FISH)	12 (21)	11 (22)

Abbreviations: FISH, fluorescence *in situ* hybridization; ISS, International Staging System; MPD, maximum planned dose

* Four patients presented with serum creatinine above 3.0 mg/dL at the time of initial diagnosis, however, all had serum creatinine < 2.5 mg/dL at the time of first treatment.

Table II

Grades 3–4 adverse events for patients treated at MPD (N=49)

Event	Grade 3, n (%)	Grade 4, n (%)
Hematologic		
Anemia	1 (2)	1 (2)
Neutropenia	7 (14)	4 (8)
Thrombocytopenia	5 (10)	1 (2)
Cardiovascular		
Atrial fibrillation	1 (2)	0
Hypotension	6 (12)	0
Syncope	1 (2)	0
Thrombosis (vascular access-related)	1 (2)	0
Dehydration	1 (2)	0
Pulmonary		
Pneumothorax	1 (2)	0
Infectious		
Pneumonia *	1 (2)	1 (2)
Cellulitis	2 (4)	0
Urinary tract infection	1 (2)	0
Gastrointestinal		
Anorexia	1 (2)	0
Nausea	1 (2)	0
Constipation	1 (2)	0
Constitutional		
Fatigue	5 (10)	0
Insomnia	1 (2)	0
Diaphoresis	1 (2)	0
Renal/Electrolytes		
Hypophosphatemia	1 (2)	0
Hypokalemia	2 (4)	0
Renal failure	1 (2)	0
Endocrine		
Hyperglycemia	0	1 (2)
Hypoglycemia	0	1 (2)
Dermatologic		
Rash (Hand-foot skin reaction) **	3 (6)	0
Neurologic		

Event	Grade 3, n (%)	Grade 4, n (%)
Sensory neuropathy***	4 (8)	2 (4)

* One patient died of bilateral pneumonia after cycle #5 of CVDD therapy (Grade 5).

** Grade 2 hand-foot syndrome was seen in 6 patents (12%).

*** Grade 2 sensory neuropathy was seen in 19 patients (39%).

Table III

Best response to CVDD chemotherapy

	Response, n (%)		
	PR	VGPR	CR
All patients (n=58)	54 (93%)	39 (67%)	20 (35%)
High-risk (n=12)	12 (100%)	10 (83%)	7 (58%)

Abbreviations: CR, complete response; PR, partial response; VGPR, very good partial response

Table IV

Selected phase 1 and 2 studies of triplet and quadruplet novel agent containing regimens for transplant eligible patients with newly diagnosed multiple myeloma (data on comparator arm for triplet vs. quadruplet are not shown)

Regimen/N/Study design/	References	Responses				Survival		Toxicity	Dose modifications/reductions
		sCR	CR/nCR	VGPR	ORR	PFS	OS		
VDD (n=40)/Phase 2	(12)	NR	37.5%	57.5%	85%	92.5% at 1-yr	97.5% at 1-yr	G2 neuropathy 7.5%, G3 palmar-plantar erythrodysesthesia 2.5%, G3 fatigue 12.5%, G3/4 thromboembolic events 10%	PLD 45%, bortezomib 40%
CRd (carfilzomib) (n=53)/Phase 1/2	(36)	42%	62%	81%	98%	92% at 2-yr	NR	G3/4 neutropenia 17%, G3/4 thrombocytopenia 17%, G3/4 DVT/PE 10%, no G3/4 neuropathy	Required in 31%
RVD (n=66)/Phase 1/2	(4)	NR	39%	67%	100%	75% at 18-m	97% at 18-m	G3 sensory neuropathy 2%, G3 fatigue 3%, G3/4 neutropenia 10%, G3/4 DVT/PE 5%	Bortezomib 44%, lenalidomide 35%
CRd (cyclophosphamide) (n=53)/Phase 2	(37)	NR	13%	47%	85%	Median 28 m	87% at 2-yr	Nearly 60% G3/4 neutropenia, G3/4 fatigue > 10%, G3/4 thrombosis > 10%, no G3/4 neuropathy	Lenalidomide 64%, cyclophosphamide 53%
CyBorD (n=33)/Phase 2	(8)	NR	39%	61%	88%	NR	NR	G3/4 thrombocytopenia 25%, G3/4 neutropenia 13%, G3 neuropathy 7% (G4 was 0%)	Bortezomib 27%, cyclophosphamide 21%
VDOR (n=25)/Phase 1, multi-center (EVOLUTION)	(7)	20%	40%	68%	96%	NR	NR	2 DLTs (G4 neutropenia, G4 herpes zoster), G3/4 neuropathy 16%	NR
VDOR (n=48)/Phase 2, multi-center, randomized (EVOLUTION)	(33)	15%	25%	58%	88%	86% at 1-yr	92% at 1-yr	G3/4 neutropenia 44%, G3/4 neuropathy 13%, G3/4 fatigue 17%, G3/4 thrombosis 2%	NR
RVDD (n=74)/Phase 1/2	(38)	15%	35%	65%	95%	80.8% at 18-m	98.6% at 18-m	G3 pneumonia 13.9%, G3/4 neutropenia 19.5%, G3 neuropathy 5.6%, G1/2 palmar-plantar erythrodysesthesia 25% (G3 was 0%), G3 PE/DVT 2.8%	NR
VTDC (n=49)/Phase 2, randomized	(32)	NR	44%	25%	96%	Median 23.5 m	79.7% at 3-yr	G3/4 neutropenia 18%, G3 anemia 18%, G3 neuropathy 8%, G3 fatigue 8%, G3 thrombocytopenia 6%	Discontinuation 6%, dose reduction: bortezomib 20%; thalidomide 24%; cyclophosphamide 2%; dexamethasone 8%

Regimen/N/Study design/	References	Responses				Survival		Toxicity	Dose modifications/reductions
		sCR	CR/nCR	VGPR	ORR	PFS	OS		
CVDD (n=58)/Phase 1/2	Nishihori et al. (current study)	19%	35%	67%	93%	Median 31 m	91.1% at 2-yr for standard-risk and 88.9% at 2-yr for high-risk group	G3/4 neutropenia 22%, G3/4 thrombocytopenia 12%, G3/4 neuropathy 12%, G3 fatigue 10%, G3/4 infection 10% at MPD dosing	Bortezomib 45%, PLD 29%, cyclophosphamide 7%

Abbreviations: CR, complete response; CRd, carfilzomib, lenalidomide, dexamethasone; CVDD, cyclophosphamide, bortezomib, liposomal doxorubicin, dexamethasone; CyBorD, cyclophosphamide, bortezomib, dexamethasone; DL-T, dose-limiting toxicity; DVT, deep venous thromboembolism; G, grade; m, month; MPD, maximal planned dose; nCR, near complete response; NR, not reported; ORR, overall response rate; OS, overall survival; PE, pulmonary embolism; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; RVD; lenalidomide, bortezomib, dexamethasone; RVDD, lenalidomide, bortezomib, pegylated liposomal doxorubicin, dexamethasone; sCR, stringent complete response; VDD, bortezomib, pegylated liposomal doxorubicin, dexamethasone; VGPR, very good partial response; VTDC, bortezomib, thalidomide, dexamethasone and cyclophosphamide