

Treatment Options for Relapsed and Refractory Multiple Myeloma

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Abstract

Treatment options for patients with relapsed myeloma have benefited from the development of new targeted agents. The use of bortezomib, thalidomide, and lenalidomide have dramatically changed outcomes for patients with relapsed myeloma. New agents are also in development, on the basis of preclinical rationale, as well as combinations of conventional and novel agents. Together each of these treatment approaches are being tested in phase I, II, and III clinical trials, with the goal of prolonged duration of remission and, ultimately, improved overall survival. *Clin Cancer Res*; 17(6); 1264–77. ©2011 AACR.

Introduction

Multiple myeloma (MM) is a malignancy of clonal plasma cells characterized by the presence of paraproteinemia, destructive bone disease, hypercalcemia, renal failure, and/or hematologic dysfunction (1). Although MM is rarely, if ever, cured, high-dose melphalan and autologous transplant prolong survival compared with standard chemotherapy (2). The growth and resistance to treatment of malignant plasma cells are dependent, in part, upon the interaction between the bone marrow microenvironment and the clonal plasma cells themselves. Indeed, the bone marrow microenvironment seems to be key, supporting the growth of myeloma by secreting growth and antiapoptotic cytokines such as interleukin-6 (IL-6), TNF α , insulin like growth factor-1 (IGF-1), and VEGF (3). In addition, direct interaction of the bone marrow microenvironment with MM through integrins and cell adhesion molecules promotes growth, inhibits apoptosis, and is responsible for resistance to conventional chemotherapy and corticosteroids (4). Novel agents that target both the MM cell and bone marrow microenvironment interaction (5) are essential in order to effect meaningful remissions and responses for most patients. The development of bortezomib, thalidomide, lenalidomide, and other new targeted molecules represents a paradigm shift in the treatment of MM (6, 7). In this review, we discuss the preclinical rationale, derived clinical studies, and combination strategies in the context of new drug development for relapsed and refractory MM.

Plasma cells form an important central function in the context of our normal immune system. They are the cells that are responsible for both short- and long-lived antibody responses following antigenic stimulation. Normally, clones of plasma cells come and go via immune regulatory pathways that include the local secretion of cytokines and stromal factors, which are necessary for the survival of plasma cells and for antibody secretion. The clonal evolution of a malignant plasma cell is thought to occur when primary genetic events transform a normal postgerminal center B cell into the malignant plasma cell. Functionally, these cells are no longer regulated by normal senescence mechanisms, with the net result being the development of an enlarging clone of cells that support their own growth and proliferation via local secretion of cytokines such as IL6, IGF-1, TNF- α , and others that are secreted by plasma cells themselves or by the stromal microenvironment within the bone marrow. Over time, additional genetic events occur that further provide the impetus for growth and proliferation, which eventually lead to drug resistance (8).

Using simple tests, such as the secretion of β -2-microglobulin (β 2M) and albumin, it is possible to clinically stage patients at the time of diagnosis; but this basic staging system has potential pitfalls and does not necessarily represent the biologic heterogeneity of myeloma at the time of initial diagnosis and, indeed, at relapse (9). The use of conventional cytogenetics and FISH allows for better identification of subsets of patients with different biology. For example, patients with any cytogenetic abnormality by metaphase analysis (which can occur in about 15% of newly diagnosed patients) are known to have a more proliferative plasma cell clone, and have a poorer overall prognosis (10). Additional groups of patients can be identified using FISH, and these include the presence of translocation (4;14; overexpression of FGFR3), (14:16; overexpression of c-maf), (14:20; overexpression of c-maf), deletion of 17p (deletion of p53), and hyperdiploidy (increase in overall ploidy, which is represented by addition of odd numbered chromosomes; refs. 11, 12).

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Cells harboring these translocations or deletions, save the presence of hyperdiploidy, are known to be associated with a more proliferative MM and, thus, are typically associated with poorer overall prognosis.

More recently, Zhan and colleagues have proposed a gene expression profile on the basis of a molecular characterization model, which has identified 7 genetic subsets of myeloma, which include the HY group (hyperdiploid), the MF group (maf overexpression), the MS group [fibroblast growth factor receptor 3 (FGFR3) overexpression], the PR group (proliferative), ME (myeloid), CD1 and CD2 [overexpression of cyclin dependent kinase 1 (CDK1) and CDK2, respectively; ref. 13]. Although they remain research tools, these genetic subsets of MM likely have real implications on prognosis, response to and durability of therapy, and are increasingly being used in the era of novel targeted agents to shape the decisions being made about approaches to therapy in the induction therapy setting, as well as in the relapsed and refractory disease setting (14).

Relapse Definition

The definition of relapsed and/or relapsed and refractory MM is best understood in the broader context of disease progression. In conjunction with the Myeloma Working Committee of the Autologous Blood and Marrow Transplant Registry (ABMTR) and International Bone Marrow Transplant Registry (IBMTR), the European Group for Blood and Marrow Transplantation (EBMT) proposed criteria to standardize the interpretation of disease progression and, thus, to provide consistency across clinical trials at different study centers (15). Relapse from a complete response (CR) is defined as reappearance of the serum or urinary paraprotein, $\geq 5\%$ bone marrow plasma cells, new lytic bone lesions and/or soft tissue plasmacytomas, an increase in size of residual bone lesions, and/or development of hypercalcemia (corrected serum calcium >11.5 mg/dL) not attributable to another cause. Criteria for progressive disease (PD), when a CR has not been achieved, include new or expanding bone lesions, hypercalcemia, and a $>25\%$ increase in serum monoclonal paraprotein concentration, 24-hour urinary light chain excretion, or plasma cells within the bone marrow. Similar criteria for PD and relapse from CR have been outlined by the International Myeloma Working Group (IMWG; ref. 16). Relapsed MM refers to the circumstance wherein a patient treated to the point of maximal response experiences PD, whereas refractory MM refers to a clinical scenario in which a patient is either unresponsive to current therapy or progresses within 60 days of last treatment. Patients who fail to achieve any response to induction therapy [$<$ minimal response (MR)] and then progress on therapy are especially challenging and fall into the category of patients with primary refractory myeloma. Meanwhile, relapsed and refractory MM describes an individual who previously achieved at least a MR, experiences PD,

receives salvage therapy, and is either unresponsive to salvage therapy or progresses within 60 days of last treatment (17).

For more than 20 years, conventional chemotherapy and high-dose therapy with either autologous or allogeneic stem cell support have been used in the management of relapsed and/or refractory MM. Regimens based on conventional chemotherapy have included high-dose dexamethasone (18, 19); vincristine, doxorubicin, and pulsed high-dose dexamethasone (VAD; refs. 20–24); vincristine, melphalan, cyclophosphamide, prednisone, vincristine, carmustine, doxorubicin, and prednisone (VMPC/VBAP; ref. 25); and doxorubicin, vincristine, dexamethasone, etoposide, and cyclophosphamide (CEVAD; ref. 26). The use of melphalan as high-dose therapy in relapsed and/or refractory MM, meanwhile, was introduced more than 20 years ago, first by McElwain and colleagues (27), and then, further developed by Barlogie and colleagues, who showed that myeloablative doses of melphalan with appropriate hematopoietic stem cell support could overcome resistance to conventional-dose chemotherapy in this group of patients (28, 29). Available data on second autologous transplants for relapsed patients suggest that these procedures are relatively well tolerated, with a 100-day mortality of $<10\%$ (30–33). Recent studies using second salvage transplants include a sizeable proportion of patients who have received novel agents in the induction setting. The overall response rates (ORR) in studies done in the past 5 years range from 55 to 69% (30, 31, 33, 34). However, owing to the small nature of these studies, it is challenging to identify the most important factors in selecting ideal candidates for a salvage auto-stem cell transplant (SCT). A recent study suggests that a relapse-free survival of >18 to 24 months after the first auto-SCT is the most reliable predictor of clinical outcome after a second auto-SCT (35). Although no official guidelines exist, the general consensus is that a salvage transplant with the intent of inducing long-term remission should be offered only to those patients who had a durable response for at least 24 months after their first auto-SCT.

In an effort to enhance the outcomes for patients with myeloma, the use of allogeneic transplant for individuals with a human leukocyte antigen (HLA)-matched donor has been explored extensively. Most studies evaluating its use in this setting show long-term disease-free survival of 10 to 20%, with a significant fraction of patients developing significant chronic graft-versus-host disease (GvHD), other treatment-related toxicities, or relapse (36, 37). Even among patients with biologically poor-risk disease as defined by International Staging System or cytogenetics, few patients are ultimately cured with allogeneic transplant (38). Given these significant limitations, and no randomized data suggesting any improvement in survival, the use of allogeneic transplant for the management of relapsed myeloma should be discouraged until more effective and less toxic approaches are established.

The emergence of novel therapies over the past decade has dramatically altered the therapeutic landscape for

Table 1. Novel Agents in Relapsed and/or Refractory Multiple Myeloma

Agent	Class	Anti-MM effects	Response rate		Potential toxicities
			Single agent	Dexamethasone (20 to 40 mg)	
Thalidomide (Thalomid)	IMiD	Decreased adhesion, cytokine production, angiogenesis, increased antimyeloma immunity	30% (CR-nCR < 5%)	50% (CR-nCR < 5%)	Teratogenicity, PN, sedation, rash, constipation, VTE
Bortezomib (Velcade)	Proteasome inhibitor	Decreased adhesion, cytokine production, angiogenesis, NFκB, DNA repair	30 to 43% (CR-nCR 10%)	40 to 55% (CR-nCR 10 to 15%)	Fatigue, PN, GI toxicity, decrease in neutrophils, platelets, and lymphocytes
Lenalidomide (CC-5013; Revlimid)	IMiD	Decreased adhesion, increased T-cell proliferation, NK cell cytotoxicity, IFN-γ and IL-2	25 to 40% (CR-nCR 6%)	65 to 70% (CR-nCR 19%)	Myelosuppression, VTE, rash, fatigue, diarrhea

GI, gastrointestinal; PN, peripheral neuropathy; IFN, interferon.

relapsed and refractory MM (Table 1). Indeed, the ability of the immunomodulatory drugs (IMiD) thalidomide and lenalidomide and the first-in-class proteasome inhibitor bortezomib to overcome drug resistance was clearly shown in preclinical models and confirmed in the context of clinical trials leading to U.S. Food and Drug Administration (FDA) approval of these compounds in the treatment of MM. Moreover, ongoing laboratory and clinical investigations are evaluating new IMiDs and second-generation proteasome inhibitors, as well as other classes of compounds that target specific pathways involved in the pathophysiology of MM. This review focuses on the role of novel agents in the treatment of relapsed and refractory MM, with discussion of other emerging compounds that may yet further impact the field.

Specific Therapeutic Agents

Thalidomide. Thalidomide was the first novel agent to be evaluated in relapsed and refractory patients, and many

pilot studies and retrospective analyses have since been reported (39–41). The recent systematic review published by Glasmacher and colleagues showed that thalidomide alone produced partial remission (PR) or better in 30% of relapsed patients, with a 1-year survival of 60% and median survival of 14 months (41). Toxicities included sedation, constipation, and increased risk of venous thromboembolism (VTE), as well as peripheral neuropathy, which occurred more frequently if the daily dose exceeded 200 mg or for durations of therapy ≥6 months (42, 43). Several investigators have noted that the addition of dexamethasone increases the ORR to 50%, with variable remission duration and survival durations seen, and another large systematic review has confirmed these findings (44).

Thalidomide has also been combined with conventional cytotoxic drugs, such as alkylating agents (45–53) and anthracyclines (54, 55), as well as with novel agents such as bortezomib (56, 57), in relapsed and/or refractory MM (Table 2). Combination therapy with thalidomide reliably results in ORRs of 60 to 75%, with CR rates of

Table 2. Selected Thalidomide Combinations in Relapsed and/or Refractory Multiple Myeloma

Author and year	No. patients	Regimen	Percent ORR	Percent CR-nCR rate	Median PFS (months)	Median OS (months)
Kropff et al. (45), 2003	60	Hyper CDT	72	4	11.0 (EFS)	19.0
Hussein et al. (54), 2003	49	PLD-T	74	20	—	—
Garcia-Sanz et al. (47), 2004	71	Thal CyDex	57	2	—	—
Offidani et al. (55), 2006	50	T/PLD/D	76	32	22.0	NYR
Palumbo et al. (53), 2006	24	MPT	42	12.5	9.0	14.0

T, thalidomide; C, cyclophosphamide; D, dexamethasone; V, vincristine; PLD, pegylated liposomal doxorubicin; P, prednisone; M, melphalan; CR, complete remission; nCR, near CR; PFS, progression-free survival; OS, overall survival; EFS, event free survival; NYR, not yet reached.

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approximately 10 to 20% in several phase I-II studies. One case-matched study by Offidani and colleagues compared thalidomide + dexamethasone + liposomal pegylated doxorubicin (ThaDD) with thalidomide + dexamethasone alone, with ThaDD producing a higher overall and CR rate than thalidomide + dexamethasone (92% and 30% versus 63% and 10%, respectively) and better median progression-free survival and overall survival (OS) with ThaDD (21 versus 11 months, 35 versus 20 months, respectively; ref. 58).

Thalidomide combinations carry an increased risk of VTE, which requires some form of prophylaxis. Individuals with a prior history of VTE should be fully anticoagulated, as should patients with other risk factors for the development of VTE. The use of aspirin, low molecular weight heparin (LMWH), and warfarin have all been evaluated (59), and the IMWG has published guidelines on the basis of a risk assessment model; specifically, LMWH, equivalent to enoxaparin 40 mg per day, has been recommended for patients with more than 1 risk factor, whereas aspirin (ASA) can be considered for those with lower risk profiles (60). In a randomized trial from Palumbo and colleagues, patients who were receiving IMiD-based therapy (including thalidomide) were randomized to receive either LMWH, warfarin, or ASA. In this trial, patients who received bortezomib-containing regimens were used as a "low-risk" group for comparison. There was no statistically significant difference in incidence in VTE among the 3 randomized arms, and all 3 arms had a low incidence of VTE, supporting the equivalence and utility of ASA as a convenient oral antithrombotic agent in this setting (61).

Bortezomib. Bortezomib is a first-in-class proteasome inhibitor with potent antimyeloma activity as a single agent (6, 62, 63). The large randomized APEX trial showed the superiority of bortezomib given intravenously on days 1, 4, 8, and 11 of a 21-day cycle over pulse dexamethasone in MM patients with relapsed and/or refractory disease who had received no more than 3 prior treatment regimens. The ORR (defined as partial response or better) was 38%, and median time to progression (TTP) was 6.2 months, compared with only 18% and 3.5 months with high-dose

dexamethasone at the time of the first analysis (64). Further follow-up yielded a response rate of 43% with bortezomib, and a longer median OS of 29.8 versus 23.7 months for the high-dose dexamethasone treated patients, despite the fact that more than 60% of patients in the dexamethasone arm were allowed to crossover to receive bortezomib (65). Among a subset of patients treated in first relapse, the ORR for the bortezomib group was 51% (65).

In the initial phase II studies, dexamethasone, usually at a dose of 20 mg on the day of and day after each bortezomib dose, could be added for a suboptimal response or progression, but was not given concomitantly from the start of therapy, with an improvement in the degree of response reported in 18 to 39% of patients (66). Two smaller single-arm phase II trials in relapsed and refractory patients have described the use of bortezomib ± dexamethasone from the onset of therapy, with ORRs ranging from 54 to 74%, with a CR rate of 7% in both (67, 68).

The toxicity profile of bortezomib has been well characterized and includes nausea, diarrhea, cyclic reversible thrombocytopenia, fatigue, and peripheral neuropathy (6, 62–64, 69). Peripheral neuropathy occurs in about one third of patients and can be painful. Dose modification or discontinuation of bortezomib is required for moderate or severe neuropathy, especially if associated with pain; the neuropathy usually improves or resolves in a high proportion of affected individuals, although often over several months (70).

Bortezomib is an attractive agent to use in combination with other drugs, because of its mild and reversible myelosuppression, ease of use in renal insufficiency (71, 72), and lack of thrombogenicity (73). Many bortezomib combinations have been evaluated in phase I-II trials, summarized in Table 3; refs. 56, 57, 74–83). These combinations generally produce high ORRs, in the range of 50 to 80% with CR and/or near CR (nCR) rates of 15 to 30%, with encouraging duration of response and OS. For example, 1 large randomized trial comparing bortezomib alone with bortezomib + pegylated liposomal doxorubicin showed the superiority of the combination in terms of TTP (9.3 versus 6.5 months) and also OS, although the increase in ORR was more modest (52% versus 44%; ref. 84).

Table 3. Selected Bortezomib Combinations in Relapsed or Relapsed and Refractory Multiple Myeloma

Author and year	No. patients	Regimen	Percent ORR	Percent CR-nCR rate	Median PFS (months)	Median OS (months)
Pineda-Roman et al. (56), 2008	85	VTD	63	22	—	22
Jakubowiak et al. (75), 2005	20	VDD	56	33	—	—
Biehn et al. (76), 2007	22	B + PLD	63	36	9.3 (TTP)	38.3
Popat et al. (78), 2005	22	B + iv Mel ± Dex	43	5	6.8 (TTP)	—
Terpos et al. (79), 2005	60	VMPT	59	11	9.5	—
Reece et al. (139), 2008	13	B+Cy+P	85	54	>12	>12

V, bortezomib (Velcade); T, thalidomide; A, doxorubicin; D, dexamethasone; Dox, pegylated liposomal doxorubicin; PLD, pegylated liposomal doxorubicin; Mel, melphalan; Cy, cyclophosphamide; PFS, progression-free survival; P, prednisone.

Preclinical studies have shown that many new investigational antimyeloma agents show at least additive benefits when combined with bortezomib, setting the stage for a number of ongoing phase I-II clinical trials of such combinations (Fig. 1).

Lenalidomide. Lenalidomide is the most recent novel agent approved for relapsed and refractory MM in the United States and Europe. Approval was based on the results from 2 parallel trials, done in each of these jurisdictions, in which lenalidomide + dexamethasone was compared with dexamethasone alone in patients with progressive myeloma who had received 1 to 3 prior regimens. The dose of lenalidomide administered was 25 mg, days 1 to 21 of a 28-day schedule, with pulse dexamethasone given days 1 to 4, 9 to 12, and 17 to 20 for the first 4 cycles; subsequently, the dose of dexamethasone was decreased to only days 1 to 4 per cycle (85, 86). Also, patients enrolled into these studies had to be tolerant of high-dose dexamethasone. The results of the 2 trials were identical, with ORRs of 60 and 61% for lenalidomide + dexamethasone, compared with 20 and 24% with high-dose dexamethasone as a single agent. The median TTP was approximately 11 months in both trials, whereas the OS with the combination was not yet reached in the North American trial (MM-090) at the time of last report (85), it was 29.6 months in the European trial (MM-010; ref. 86). Moreover, the benefit of lenalidomide + dexamethasone was apparent despite extensive crossover of patients from the dexamethasone arm to lenalidomide-based therapy, similar to the APEX trial.

Lenalidomide avoids some of the more troublesome toxicities of thalidomide, such as somnolence, constipation, and significant peripheral neuropathy. However, it is associated with an increased risk of VTE, just like thalidomide, and thromboprophylaxis is required, typically with ASA (59, 60). A retrospective analysis from Nooka and colleagues sought to validate the IMWG guidelines for lenalidomide thromboprophylaxis (87). In this series, all patients being treated with lenalidomide in the relapsed or refractory setting were evaluated, and the incidence of VTE, with ASA prophylaxis, was low. Among patients who did

develop VTE, each of them had >1 risk factor, suggesting that their VTE episode was predicted by the IMWG guidelines, which would have recommended more intense prophylaxis. Further studies are ongoing to definitively address these questions, but ASA is currently the most commonly used approach in appropriate candidates.

Importantly, lenalidomide can produce neutropenia and thrombocytopenia (85, 86, 88). If significant neutropenia occurs, either the dose of lenalidomide can be reduced, or granulocyte colony stimulating factor (G-CSF) can be given while maintaining the full lenalidomide dose. In the experience reported at Princess Margaret Hospital, an average of 4 doses of G-CSF per cycle is usually sufficient and, typically, is given twice weekly starting day 15 of each cycle (89). Of note, at least when used as initial therapy, more neutropenia was observed in patients given low-dose weekly, rather than full-dose pulse, dexamethasone (90).

Experience with lenalidomide in patients with renal sufficiency is relatively limited, although the drug at reduced dose has been administered to patients with variable degrees of renal compromise without prohibitive toxicity (89, 91). Recently, the manufacturer has issued recommendations for the use of this agent on the basis of the creatinine clearance, subsequent to pharmacokinetic studies in normal volunteers.

Exploration of lenalidomide-based combinations, both with conventional agents and new agents, has now been reported. These include combinations with doxorubicin or pegylated liposomal doxorubicin (92, 93) and cyclophosphamide (Table 4; ref. 94). Combinations of these novel agents have also been studied in relapsed and/or refractory MM patients, often as a prelude to their use as part of first-line therapy. Lenalidomide + bortezomib ± dexamethasone has shown especially encouraging activity and excellent tolerability in this context (95). The maximum tolerated doses of this regimen were bortezomib 1.0 mg/m² on days 1, 4, 8, and 11 and lenalidomide 15 mg on days 1 to 14 of a 21-day cycle with an ORR of 60% and an encouraging median OS of 37 months. This combination has been evaluated with dexamethasone 20 mg on the day of and day after bortezomib for the first 4 cycles and 10 mg on the same days after cycle 4, with the phase II trial of

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Table 4. Lenalidomide-Based Combinations in Relapsed or Relapsed and Refractory Multiple Myeloma

Author and year	No. patients	Regimen	Percent ORR	Percent CR-nCR rate	Median TTP (months)	Median OS (months)
Schey et al. (140), 2010	31	LCD	81	36 (VGPR)	—	—
Knop et al. (141), 2009	66	LDoD	73	15	8	88% (1 year)
Reece et al. (142), 2009	15	LCP	74	45 (VGPR)	—	—
Baz et al. (92), 2006	52	LPLDViD	75	29 (nCR)	61% (1 year)	84% (1 year)
Richardson et al. (95), 2009	35	RV ± D Ph I	60 (≥MR)	8	7.7	37
Anderson et al. (96), 2009	62	RVD Ph II	69	26	12	29

Len, lenalidomide; PLD, pegylated liposomal doxorubicin; Vi, vincristine; Do, doxorubicin; D, dexamethasone; C, cyclophosphamide; P, prednisone; V, bortezomib (velcade); R, lenalidomide (revlimid); thal, thalidomide; NYR, not yet reached; Ph, Phase.

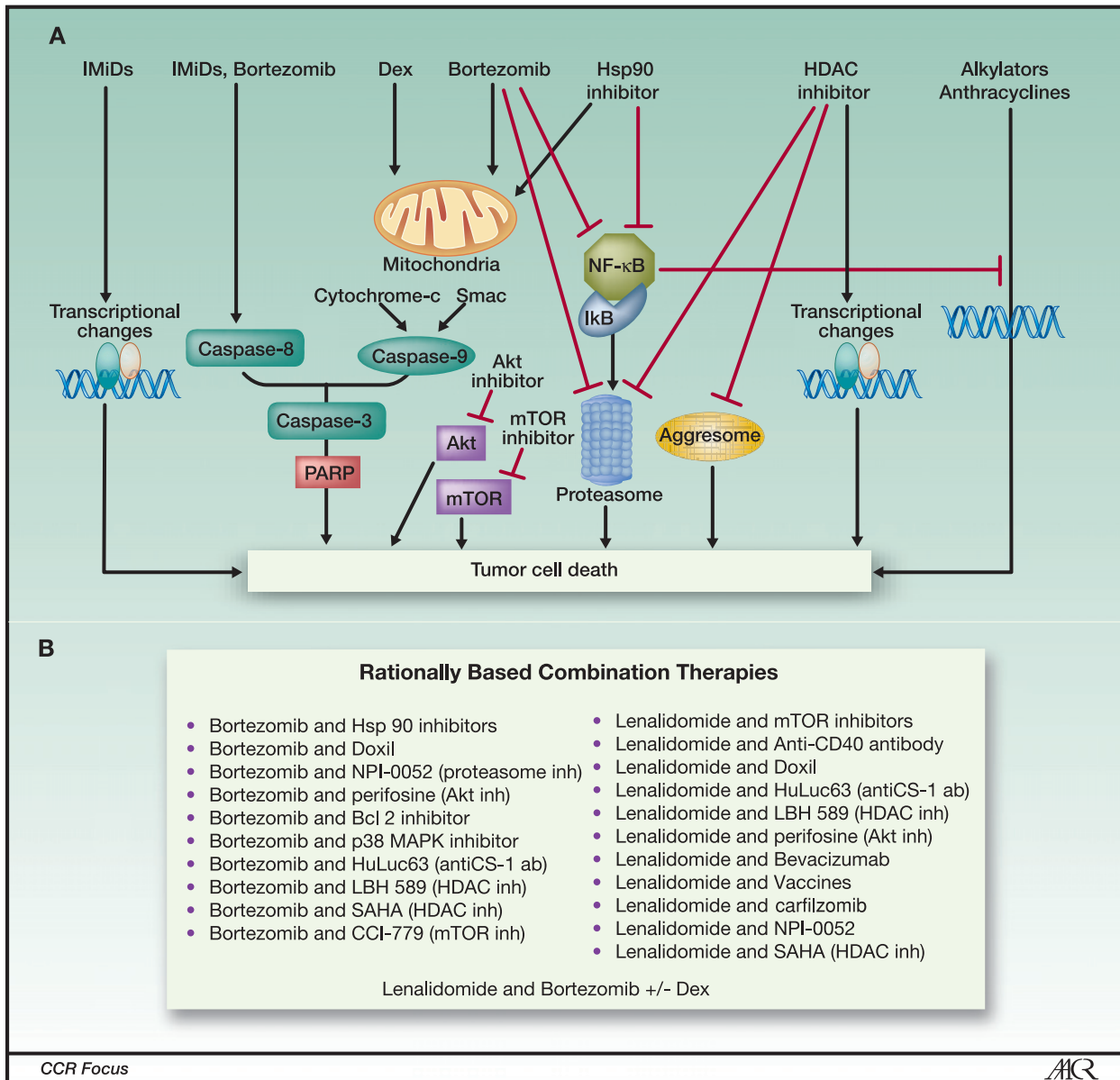


Figure 1. A, schematic of the potential benefit for combination therapy in the activation of independent proapoptotic signaling cascades, which result in synergistic tumor cell apoptosis in MM [modified with permission from Richardson et al. (97)]. B, rational combination regimens using either bortezomib or lenalidomide with novel agents based upon preclinical evidence of synergy (please see text for details).

this regimen reporting at least a PR in 54%, including near CR in 6%, very good PR (>90% reduction in serum monoclonal protein) in 30%, and MR in 18%. To date, the median duration of response is 7 cycles, whereas the TTP has not yet been reached (96).

Combination Approaches

The rationale for combination studies in relapsed disease is 2 fold. First, it is clear across most of oncology and, in particular, in hematologic malignancies that combinations are more effective than single agents at inducing responses

and, if tolerable, in achieving durable responses. Second, exposure of malignant cells to a single agent often results in preferential overactivation of alternate survival pathways, which can then be rationally targeted using other agents (Fig. 1A). This concept of induced pathway dependence (or addiction) forms the basis for many combination strategies in MM, as described below. Finally, the use of combinations should also take advantage of other potential mechanisms of action for a given single agent, which can be further enhanced when used in conjunction with another agent, as well as the avoidance of any potential overlapping toxicity (Fig. 1A; ref. 97).

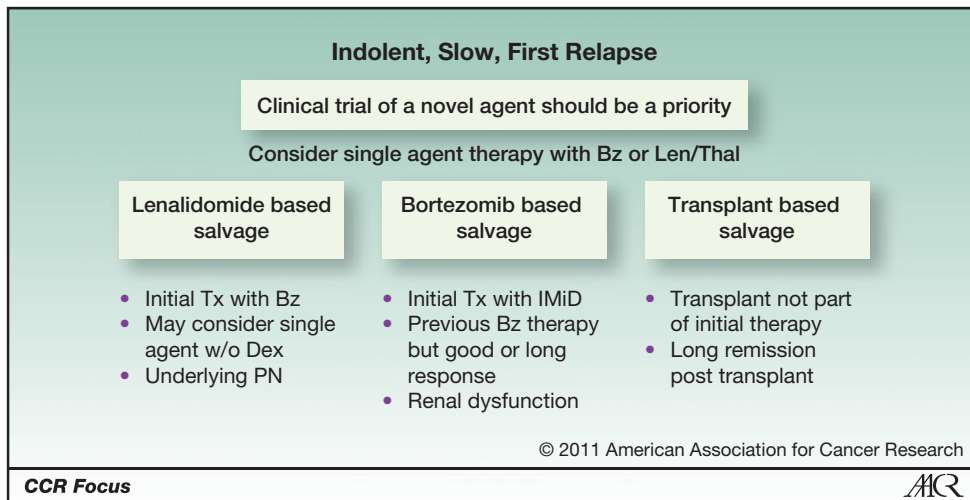


Figure 2. Possible treatment approaches for patients with relapse early in the disease course or indolent relapse.

Excitingly, most of the novel combination approaches in MM explored to date have reliably produced response in the majority of patients, and CR or nCR is not uncommon. One unresolved question in MM therapy is whether use of combinations of novel agents to achieve high response rates is better than the sequential use of these agents alone, or with a more traditional partner such as corticosteroids. Although there is no clear simple algorithm to define how a patient should be treated in the relapsed setting, some general principles can guide the choice of therapy. For patients with indolent or relapse early in their disease course, the use of single agents, depending upon what was used in their initial therapy, as well as treatment-related toxicity, is a reasonable approach (Fig. 2). Additionally for patients who did not have a transplant as part of their initial treatment, or for patients with long duration of remission following transplant, salvage autologous transplant could be considered. For patients with more advanced relapse, or with aggressive disease biology, the use of combinations of

agents or novel agents in combination with cytotoxic agents may be a more appropriate approach (Fig. 3). Even among these patients, the use of salvage transplant has a role if cytopenias are limiting treatment options, as long as some form of maintenance therapy is used afterward in an effort to stave off early or rapid relapse. Disease biology can also influence the choice of therapy for relapsed and/or refractory MM, and regimens including bortezomib or lenalidomide are preferred in individuals with the higher risk t(4;14) disease as well as the use of some form of maintenance therapy, which seems to be of greater importance among patients with biologically defined high-risk disease. Importantly, the optimal therapy of patients with p53-positive MM, who usually derived short benefit from available therapies outcomes, is not known at this time and, thus, for these patients, aggressive combination therapy with aggressive maintenance treatment may be warranted (98). More sophisticated biologic correlates for the selection of treatment are obviously desirable and now under study.

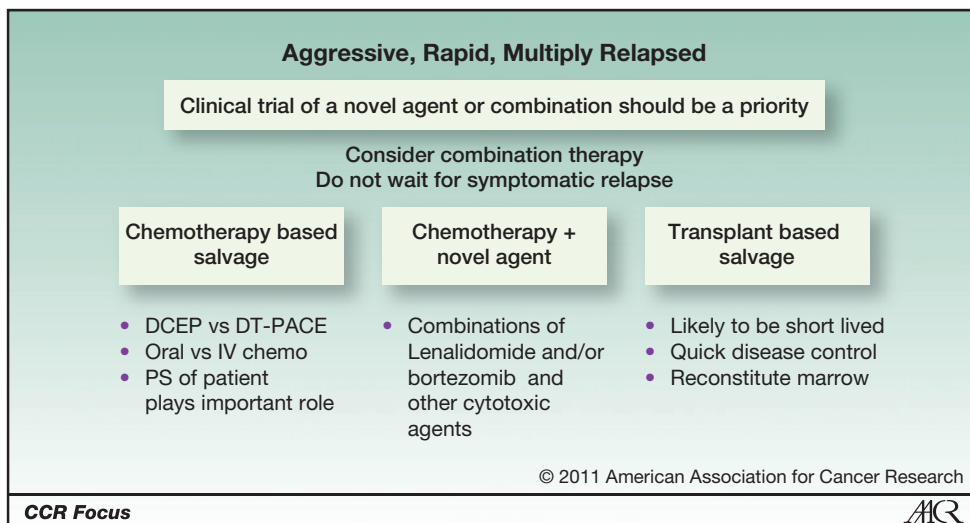


Figure 3. Possible treatment approaches for patients with aggressive relapse or relapse late in the disease course.

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Proteasome Inhibitor–Based Strategies

In addition to the effects of single-agent proteasome inhibitors on plasma cell apoptosis, a number of novel combination strategies are predicted by preclinical data and seem to warrant further clinical study over and above those shown previously. The first of these strategies involves the combination of the HSP inhibitor 17AAG with bortezomib. Early data from Mitsiades and colleagues suggested that exposure to bortezomib resulted in a compensatory stress response that included early and rapid upregulation of HSP 90, in addition to HSP 27 and other markers of cellular stress (99). *In vitro* and *in vivo* work further showed that the combination of an HSP 90 inhibitor with bortezomib seemed to induce significant regression of tumors in xenograft models. A phase I clinical trial conducted combining tanespimycin with bortezomib showed not only an encouraging ORR (57%), but also that patients with bortezomib-resistant disease responded, suggesting reversal of bortezomib resistance (100). Additionally, other HSP inhibitors are in development, and, given the preclinical data suggesting that overexpression of HSPs are found broadly in cancer cells, the concept of combinations of agents using an HSP inhibitor as part of the therapy is being tested in multiple different tumors (101–104).

Additional data are emerging combining bortezomib with histone deacetylase (HDAC) inhibitors (HDACi; specifically, vorinostat, LBH 589, and depsipeptide), and in preclinical models these have shown significant synergy. Mechanistically this synergy is thought to be related to the effects of HDACi on HDAC 6, which is critical to the function of an alternative pathway of protein catabolism, the aggresome-autophagy pathway (105). When patients are exposed to proteasome inhibition, the alternative pathway is upregulated (specifically the aggresome pathway), and protein catabolism occurs via this alternative pathway. The combination of proteasome inhibition and HDAC 6 inhibition [accomplished using HDACi, tipifarnib (106), or the HDAC6 specific agent tubacin (107)] results in preclinical synergy, a concept which is now being evaluated clinically. Preliminary data from phase I studies combining the HDACi vorinostat with bortezomib showed significant responses, and among the patients who were defined as bortezomib resistant, the ORR was 30% (108, 109). A trial from Prince and colleagues also evaluated the efficacy of the combination of the HDACi romidepsin (also known as depsipeptide) with bortezomib and reported encouraging responses (110). Further studies combining vorinostat with bortezomib are being tested as part of a larger phase III trial, as well as combinations of LBH 589 (also known as panobinostat) with bortezomib. The combination of LBH589 and bortezomib in the setting of relapsed and refractory MM has been promising. In a phase I-II study from San Miguel and colleagues, the ORR (defined as MR or better) for the phase I portion of the trial was 70%, with 60% of patients who were refractory to bortezomib responding to the combination. These trials, in aggregate,

clinically validate the combination of bortezomib and an HDACi, and the results of the larger phase III studies are eagerly awaited.

The phosphoinositide 3-kinase (PI3K)/Akt axis represents a novel target in malignant plasma cell biology, as the cellular response to exposure of commonly active antimyeloma agents is activation of the PI3K pathway (111). To date, clinical data using a true PI3K inhibitor in myeloma are scarce, though several inhibitors are in early stage development. Preclinical data from Hideshima and colleagues have also explored other potential survival responses among malignant plasma cells, following treatment with bortezomib (112). Given with dexamethasone, perifosine generated 35% MR or better in heavily pretreated patients with relapsed and refractory, refractory MM (113). As described previously, on the basis of preclinical data suggesting that the cellular response to bortezomib results in activation and upregulation of *p*-Akt (112), the combination of bortezomib and perifosine has been tested in a phase I-II trial, which showed an ORR of 38% in relapsed and refractory patients who had received a median of 5 prior lines of therapy including bortezomib, with encouraging OS seen (median 25 months; ref. 114). In another phase I-II trial, the combination of perifosine and lenalidomide-dexamethasone was also tested, and the ORR for this combination was 70% among a group of patients who had received a median of 2 prior lines of therapy (115). Further studies are planned using this combination of agents with the intent of enhancing the efficacy of bortezomib and/or lenalidomide and confirming clinical benefit.

Immunomodulatory Agent–Based Strategies

The effects of thalidomide and lenalidomide on immune function have been shown in a number of animal and preclinical models and include enhancement of natural killer (NK) cell function, CD8+ T-cell activation, and increased secretion of IL-2 and interferon- γ (116, 117). Data with antibodies directed against plasma cell and B-cell antigens, such as CD40 and CS1, were evaluated in preclinical models with lenalidomide and showed significant synergy (118, 119). Experience with the antibody SGN-40 in conjunction with lenalidomide showed that there was enhancement in peripheral blood mononuclear cell proliferation and autologous myeloma cell kill when the 2 agents were combined together (120). Experience with the potent CS1 antibody elotuzumab (known as Huluc63) shows that this target is relatively plasma cell specific and that the functional activity of the CS1 antibody requires NK cells to be present for activity (121, 122). When lenalidomide is combined with elotuzumab, the activity of the antibody is enhanced, and more myeloma cells are killed via target-specific lysis both in cell lines and in primary patient myeloma cells (123). On the basis of this preclinical foundation, several trials are currently ongoing in the context of capitalizing on this effect. The prototype for this clinical trial approach is

the combination of lenalidomide with elotuzumab (HuLuc63); in an ongoing phase I study, patients started with the full dose of lenalidomide (25 mg on days 1 to 21 every 28 days) and low-dose dexamethasone (40 mg weekly) with escalating doses of elotuzumab (124). In the phase I portion of the trial, patients received up to 20 mg/kg without experiencing dose-limiting toxicity. The ORR for the phase I study was 82%, with 95% of lenalidomide-naïve patients achieving PR or better. No significant reduction in ORR was noted among patients who had either >3 prior lines versus those who had <3 prior lines, suggesting that the novel approach of a monoclonal antibody was able to overcome resistance in heavily pretreated patients, as well as in those who were earlier in their clinical course. Furthermore, when compared with historical cohorts of patients who were treated with lenalidomide and low-dose dexamethasone, there is the suggestion that the addition of elotuzumab enhanced the ORR, although the number of patients reported to date is relatively small. Another trial combining the CD40 antibody SGN-40 with lenalidomide is also in process.

A number of groups have started to explore combinations of lenalidomide with other cytotoxic agents or small molecule inhibitors. Although combinations with cyclophosphamide and melphalan have shown activity both in the induction and the relapsed and/or refractory setting, combinations with agents such as HDACis and tyrosine kinase inhibitors have also been evaluated. The HDACis potentially offer mechanistically separate effects in combination therapy, related either to gene transcription and gene silencing or to acetylation of cytoplasmic proteins (125, 126). In terms of the latter, for example, in the setting of combination therapy with bortezomib, it is likely that the effects on HDAC6 inhibition and combined proteasome-aggresome inhibition are responsible for the preclinical and clinical synergy when these agents are combined (105, 107, 127). In combination therapy with lenalidomide, the exact mechanism of action remains unclear, but preclinical data combining vorinostat (128) and panobinostat (LBH 589) with lenalidomide have shown enhanced plasma cell death, possibly through epigenetic effects. A phase I study combining lenalidomide with vorinostat shows considerable promise (129), with another trial showing an ORR of 60% and a very good PR (VGPR) or better rate of 35% (130).

Second- and Third-Generation Agents in Development for the Treatment of Relapsed and Refractory Multiple Myeloma

The activity of proteasome inhibition and immunomodulatory agents is now established in MM therapy and is being explored in other diseases as well.

Second-generation proteasome inhibitors are now in development with different functional abilities. Specifically, PR-171 (carfilzomib) is an irreversible inhibitor of chymotryptic activity of the proteasome, the same site of

inhibition induced by bortezomib, and is currently being tested in phase I-II and III trials in MM (131, 132). Another second-generation proteasome inhibitor in earlier clinical development is NPI-0052 (133), which is also irreversible and with a more broad-ranging inhibition of all 3 enzymatic sites within the proteasome, as opposed to the single site seen with bortezomib and carfilzomib. Further testing is needed to fully establish the safety and efficacy of these new agents and to see if they have a broader therapeutic index than is seen with bortezomib, but early results seem favorable. Complementary to the development of newer proteasome inhibitors, there is the development of the new immunomodulatory agent CC-4047 (also known as pomalidomide). Data initially presented by Schey and colleagues showed favorable tolerability and activity of this agent in myeloma patients with early relapse, as well as a potent immune-activating effect (134). Another trial from the same group evaluated the safety and efficacy of alternate day pomalidomide and again showed encouraging efficacy with an improved safety profile (135). Additional trials are being done in more advanced MM to further define the efficacy and safety of this agent, with remarkably promising results to date, even in patients refractory to both bortezomib and lenalidomide (136, 137).

Summary and Conclusions

Combinations of agents in relapsed and refractory MM are clearly moving forward. Advantages of combination therapy include higher ORRs and, in many cases, better depth of responses, as well as the ability to revisit "backbone" agents used earlier in treatment. Many of these combinations are, in part, derived from informative preclinical studies and rationally designed clinical trials (Fig. 1A and B). In the balance is the concept that sequential therapy may be associated with less toxicity than is seen with combination therapy, and because few (if any) of these patients are cured of their disease, whether to treat a patient with single agents in sequence rather than combinations is an area of active study and ongoing debate. Although the complete answer to this question is unknown, what may strongly favor combinations is the fact that few diseases, including myeloma, have a single genetic or functional defect that can be addressed by a single drug (with the exception of chronic myelogenous leukemia, perhaps), and, thus, combinations of agents are much more likely to result in better disease control, especially given the intrinsic heterogeneity of MM. Second, by using combinations, complementary mechanisms of action (or induced oncogene addiction) may, in fact, become more than a laboratory phenomenon and be a clinical reality. Finally, given that the major advances in oncology seen to date have occurred as a result of combination therapy, this approach, provided the patient is not affected by excess toxicity, represents a path by which the greatest success can reasonably be anticipated. Additional preclinical studies and derived clinical trials that prove the

efficacy of combination therapy are needed in advanced MM and will likely be forthcoming in the near future to further improve patient outcome (138).

Disclosure of Potential Conflicts of Interest

S. Lonial, consultant, Millennium, Celgene, BMS, Novartis, Merck, Onyx. P.G. Richardson, consultant, Millennium, Celgene, Johnson & Johnson, Novartis. C.S. Mitsiades, consultant honoraria from Millennium Pharmaceuticals, Novartis Pharmaceuticals, Bristol-Myers Squibb, Merck & Co., Kosan Pharmaceuticals, Pharmion and Centocor; licensing royalties from PharmaMar; and research funding from OSI Pharmaceuticals, Amgen,

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