

Advances in oral therapy for multiple myeloma

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Lancet Oncol 2006; 7: 316–25

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Conventional intravenous chemotherapy regimens are toxic, cumbersome, and negatively affect patients' quality of life, with oral treatment preferable to most patients with cancer. Multiple myeloma is the second most common haematological malignant disease, but cannot be cured with conventional and high-dose chemotherapy. New oral treatments that target myeloma cells or bone marrow are being developed that are highly effective yet have low toxic effects, such as the immunomodulatory drugs thalidomide and lenalidomide. Several treatments in early development have shown antimyeloma activity, including: CHIR-258, which inhibits fibroblast growth factor receptor 3; NVP-ADW742, which inhibits insulin-like growth factor receptor 1; and PTK787, which inhibits vascular endothelial growth factor. Additional drugs aimed at switching off silenced genes include histone deacetylase inhibitors. The availability of these various oral treatments is hoped to improve regimens that, if used sequentially or in combination, offer the potential of making multiple myeloma a chronic disease, thereby extending patients' lifespans and improving quality of life.

Introduction

Conventional intravenous chemotherapy regimens frequently require the placement of indwelling catheters, which are associated with much inconvenience and severe complications that need many hospital visits or extended hospital stays, all of which adversely affect the patient's quality of life.^{1,2} Several oral chemotherapeutic drugs have shown equivalent efficacy compared with that of intravenous treatments, and offer several advantages for patients with cancer, including improved convenience, reduced number of hospital visits, and decreased pain.^{3,4} As a consequence of these factors, questionnaire-based studies have shown oral therapy to be preferred by patients with cancer (figure 1).^{5,6}

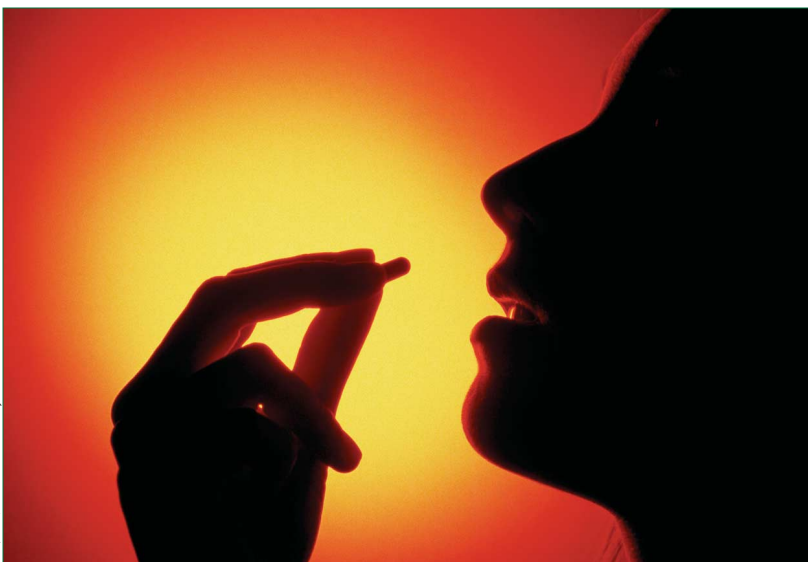
Multiple myeloma is the second most common haematological malignant disease, but remains incurable with conventional and high-dose chemotherapy. Evolving treatment options are improving outcome data, and offer the real potential for patients to have

extended lives with low levels of disease present that does not interfere with their lifestyles. Therefore, the development of low-toxic oral regimens is essential. Until recently, the primary treatment for symptomatic myeloma has consisted of intermittent oral therapy with melphalan and prednisone, dexamethasone alone, or combination chemotherapy with three or more drugs⁷ that frequently need intravenous infusions. Although higher responses (60% combination chemotherapy vs 53% melphalan and prednisone; $p < 0.0001$) are achieved with intravenous combination regimens, duration of response and overall survival are similar to that achieved with melphalan and prednisone alone.⁸

Moreover, these regimens have several disadvantages, including pain associated with use of a central venous catheter, need for continuous infusion of chemotherapy, risk of catheter-related infections, central venous thrombotic events, and potential cardiac and neurological toxic effects.^{9,10} Therefore, it is not surprising that oral melphalan became standard treatment for myeloma worldwide. However, because of the drug's well-known stem-cell toxic effects, it is unsuitable for tumour-debulking therapy before stem-cell harvest and autograft. Vincristine, doxorubicin (adriamycin), and dexamethasone (VAD)-based intravenous regimens are typically used in this setting, and an effective oral therapy to replace VAD before stem-cell harvest would offer good advantages. Dexamethasone, an oral drug, is thought to contribute much of the therapeutic benefit of VAD, and provides a suitable approach to modify with additional chemotherapeutic agents.

Several promising non-cytotoxic biological drugs with new mechanisms to target multiple-myeloma cells and to overcome resistance from conventional cytotoxic drugs have been developed, which could form the basis of oral combination regimens. Of the newer treatments for myeloma, many are given orally,¹¹ including the immunomodulatory drugs thalidomide and lenalidomide, and specific inhibitors of the tyrosine kinase

See *Lancet* 2006; 367: 825–31
for a randomised trial of
multiple myeloma



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Figure 1: Oral treatment is preferable for most patients with cancer

activity of fibroblast growth factor receptor 3 (FGFR3), insulin-like growth factor-1 receptor (IGF-IR), and vascular endothelial growth factor (VEGF).^{11,12} Clinically, these compounds have shown promising activity and tolerability in patients with relapsed, refractory disease and in those with newly diagnosed myeloma (table 1). We discuss the clinical experience to date with oral therapies for myeloma, and the emerging role of other new drugs in the management of this disease.

Oral treatments

Oral regimens for multiple myeloma include conventional chemotherapies and several new oral drugs in various stages of clinical development that selectively target specific pathways in the growth and survival of myeloma cells (figure 2, table 1). Therapeutic targets are associated mainly with plasma cells or the bone-marrow environment. Plasma-cell targets include surface proteins and cell signalling factors; targets in the bone marrow include: adhesion molecules; cytokines; signalling proteins; and factors associated with blood vessels, immune cells, and osteoclasts (figure 2).

Oral chemotherapy

Alkylating drugs

After its initial development, melphalan alone was compared with melphalan and prednisone, and although no clear advantage was noted for the combination, it has since been used widely and has been regarded the standard treatment against which to compare other therapies. Melphalan was compared with cyclophosphamide, another orally active alkylating drug, and again no differences in outcomes were recorded. However, use of oral cyclophosphamide on a weekly basis does have some advantages, including fewer stem-cell toxic effects than those with melphalan or ABCM (doxorubicin [adriamycin], carmustine [BiCNU], cyclophosphamide, melphalan), and activity as a single oral agent able to consolidate responses after combination chemotherapy. For example, results from the UK Medical Research Council (MRC) VIII myelomatosis trial^{13,14} suggested that treatments changing to weekly cyclophosphamide after starting with three cycles of ABCM are as effective as continuation of ABCM until a plateau is reached.

Dexamethasone

Glucocorticoids such as prednisone and dexamethasone are effective against myeloma, and are used extensively to treat patients with advanced disease. Dexamethasone has substantial single-agent activity and induces rapid responses in patients with previously untreated and with relapsed, refractory disease.^{15,16} Dexamethasone binds to the steroid hormone receptor in the cytosol and induces apoptosis via caspase 8, a signal that is inhibited by interleukin 6. In clinical studies,^{16,17} high-

Drug	Class	Preclinical/on-clinical testing	Tested against relapse-refractory disease	Tested against newly diagnosed disease
Thalidomide	Immunomodulatory	Yes	Yes	Yes
Lenalidomide	Immunomodulatory	Yes	Yes	Yes
SCH-66336	RAS/RAF/MAPK inhibitor	Yes	Yes	No
R115777	RAS/RAF/MAPK inhibitor	Yes	Yes	No
SAHA	Histone deacetylase inhibitor	Yes	Yes	No
PTK 787	VEGF inhibitor	Yes	Yes	No
SCIO-469	P38 MAPK inhibitor	Yes	Yes	No
Seliciclib	CDK inhibitor	Yes	No	No
NVP-ADW742	IGF-IR inhibitor	Yes	No	No
CHIR-258	FGFR3 inhibitor	Yes	Yes	No

CDK=cyclin-dependent kinase. MAPK=mitogen-activated protein kinase. VEGF=vascular endothelial growth factor.

Table 1: Current status of new oral treatments for multiple myeloma

dose dexamethasone was effective in 27–40% of patients with resistant disease. However, high-dose dexamethasone (ie, 40 mg/day) is poorly tolerated, especially in elderly patients.

VAD has been the standard approach for induction before stem-cell transplantation, but much of its effectiveness is due to dexamethasone.¹⁵ Attempts have been made to improve the effects of single-agent dexamethasone in this setting and maintain an orally active regimen at the same time. Idarubicin, an orally active anthracycline, has been used in combination with dexamethasone (ie, ZDex),¹⁸ and subsequently in combination with dexamethasone and cyclophosphamide (ie, CZDex).

However, the addition of newly available drugs such as thalidomide and lenalidomide offer the potential to substantially improve these regimens.

Immunomodulatory drugs

Thalidomide

A derivative of glutamic acid, thalidomide has shown excellent results against relapsed, refractory,^{19–23} and newly diagnosed^{24,25} disease. Thalidomide was initially considered for the treatment of myeloma, on the basis of its known antiangiogenic and immunomodulatory properties, and the observation of increased angiogenesis in the bone marrow of patients with myeloma.^{26,27} Evidence from in-vitro and in-vivo studies shows that thalidomide targets myeloma cells and the surrounding bone marrow through several different mechanisms, such as inhibition of cell adhesion to bone marrow; modulation of multiple-myeloma growth, survival, and migratory factors (ie, interleukin 6, VEGF); and enhancement of T-cell stimulation and proliferation of natural killer cells.^{28,29}

Complete, partial, and minor responses have been reported at 30–50% for single-agent thalidomide at various doses in patients with relapsed, refractory multiple myeloma.^{19–23} Subsequent assessments of

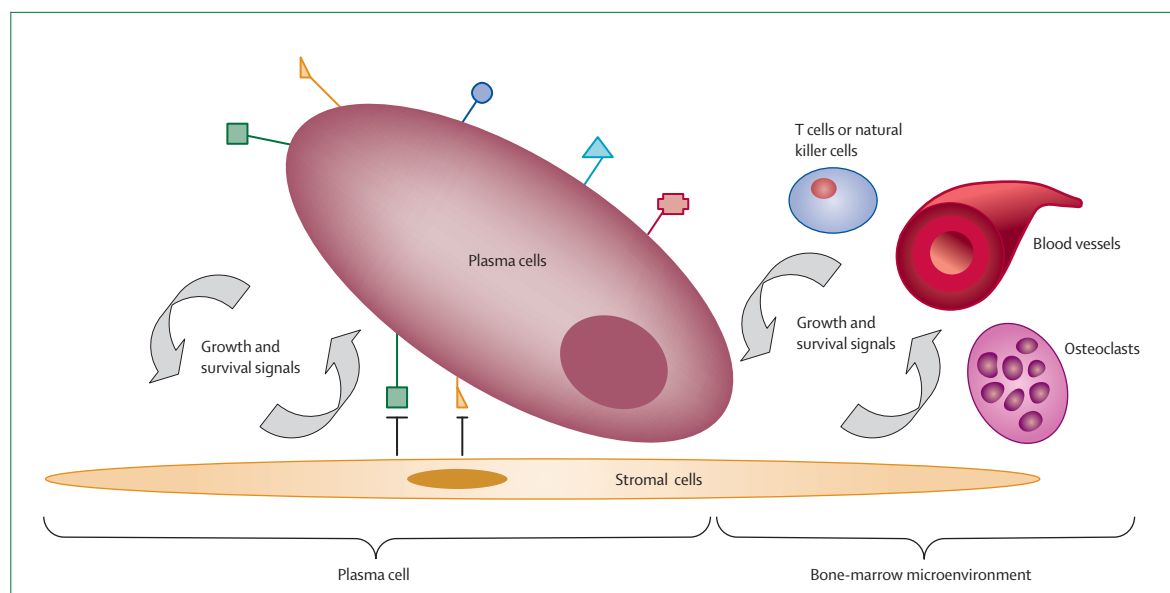


Figure 2: Potential targets for antimyeloma treatments

Surface proteins on plasma cells include: CD (cluster of differentiation) 138, HM124, vascular and neuronal cellular adhesion molecules (VCAM and NCAM), and mucin 1. Plasma-cell signalling targets include: FGFR3, IGF-IR, phosphatidylinositol-3 kinase, AKT, nuclear factor (NF) κ B, signal transducer and activator of transcription (STAT) 3, MCL1, X-box binding protein (XBP) 1, the proteasome, histone deacetylases, and heat shock proteins. Targets for the bone-marrow environment include: adhesion molecules (NCAM, VCAM); cytokines (interleukin 6, IGF-1, tumour necrosis factor, stromal cell-derived factor [SDF] 1, VEGF, basic fibroblast growth factor [bFGF]); signalling molecules (MAPK, NF κ B); blood-vessel-related molecules (VEGF, bFGF); immune cells (T cells, natural killer cells, dendritic cells); and osteoclast-related molecules (receptor-activator of NF κ B [RANK-Fc], osteoprotegerin).

single-agent thalidomide in patients with newly diagnosed disease showed about a third of patients had at least 50% reduction in paraprotein.^{24,25,30,31} In a phase II study²⁴ of response and time to disease progression with 200 mg thalidomide a day in patients with smouldering or indolent myeloma, event-free survival was 80% at 1 year and 63% at 2 years.

Synergistic activity of thalidomide in combination with dexamethasone was initially found *in vitro*. Subsequently, clinical results showed higher responses with thalidomide and dexamethasone than with thalidomide alone in relapsed, refractory myeloma^{21,22,32–34} and newly diagnosed myeloma^{24,25,30,31} (table 2).^{21,22,24,25,30–34} In relapsed, refractory disease, responses of up to 60% have been recorded.^{32–35} In these studies, the addition of dexamethasone to thalidomide reduced median time to response, and 33% of maximum responses occurred in the first 2 months of therapy.^{32,35} Compared with conventional VAD salvage chemotherapy in patients who had received one line of chemotherapy, thalidomide and dexamethasone increased progression-free survival in patients with relapsed, refractory disease (median 17 months for thalidomide and dexamethasone vs 11 months for VAD; $p=0.0024$) and 3-year survival (60% vs 26%, respectively; $p=0.0016$).³² The safety and efficacy of thalidomide plus dexamethasone have been assessed in previously untreated patients.^{25,30,31,36} Preliminary data from a phase III randomised comparison of 200 mg thalidomide a day plus 40 mg dexamethasone on days 1–4, 9–12, and 17–20 with the same regimen of

dexamethasone alone in 207 patients eligible for high-dose chemotherapy have become available.³¹ Interim analysis of 109 patients showed higher responses (ie, $\geq 50\%$ reduction in paraprotein) from thalidomide and dexamethasone than those from dexamethasone alone (80% vs 53%; $p=0.0023$; table 2).

However, combination therapy was associated with substantially more severe toxic effects—especially venous thromboembolism, including deep venous thrombosis and pulmonary embolism (14% thalidomide plus dexamethasone vs 3% dexamethasone).³¹ In a retrospective analysis,³⁷ the safety and efficacy of thalidomide or dexamethasone as a primary therapy in preparation for autologous transplantation showed a higher response than that of VAD (76% vs 52%; $p=0.0004$) and a higher reduction in myeloma cell mass (reduction in residual proteins: IgG, $p=0.02$; IgA, $p=0.03$). Moreover, consolidation therapy with thalidomide and dexamethasone is effective in patients with persistent partial response after myeloablative therapy, with more than half achieving greater than 90% reduction of paraprotein.³⁸

Other combinations of thalidomide have been tested to increase response. The CTD oral combination of 500 mg cyclophosphamide a week, 100–200 mg thalidomide a day, and 20–40 mg dexamethasone on days 1–4 and 12–15 on a 21-day cycle increases the responses obtained with thalidomide and dexamethasone, exploits the ability of the alkylator to give rise to a stable plateau phase (characterised by few

	Number of patients	≥75% decrease in paraprotein	≥50% decrease in paraprotein	≥25% decrease in paraprotein	Grade 3-4 toxic effects	Ref
Regimens for advanced disease						
200-600 mg thalidomide a day	26	..	11 (42%)	14 (54%)	Grade 3: neuropathy (7%), muscle cramps (3%), constipation (3%), somnolence (3%), rash (3%) Grade 4: none	21
200-800 mg thalidomide a day	32	..	10 (31%)	17 (53%)	>Grade 3: neutropenia (31%), neuropathy (16%), sedation (13%), constipation (6%), sinus bradycardia (6%), febrile neutropenia (6%), dyspnoea (3%), fatigue (3%), thrombosis (3%), rash (3%), vertigo (3%)	22
100 mg thalidomide a day and 40 mg dexamethasone a day; conventional chemotherapy (days 1-4 per month)	120; 120	..	62 (52%), 54 (45%)	Not recorded (for both groups)	Grade 3: neuropathy (3%), gastrointestinal (3%)	32
200-600 mg thalidomide a day and 20 mg/m ² dexamethasone (days 1-5, every 15 days)	47	..	22 (47%)	Not recorded (for both groups)	Grade 3: peripheral neuropathy (8%), deep vein thrombosis (8%), rash (4%), ileus (2%)	33
100-400 mg thalidomide a day and 40 mg dexamethasone a day (4 days per month)	20	..	12 (60%)	4 (20%)	Not specified (15%)	34
Regimens for newly diagnosed disease						
200-800 mg thalidomide a day	29	Not recorded	10 (34%)	19 (66%)	Grade 3: sedation (6%), hearing loss (3%), fatigue (3%), oedema (3%), deep vein thrombosis (3%) Grade 3-4: sinus bradycardia (3%), peripheral neuropathy (3%)	24
200 mg thalidomide a day and 40 mg dexamethasone a day (odd cycles: days 1-4, 9-12, 17-20; even cycles: days 1-4; repeat monthly)	50	26 (52%)	34 (68%)	46 (92%)	Thrombosis (12%), constipation (8%), rash (6%), dyspnoea (4%), depression (2%), sedation (2%), arrhythmia (2%), oedema (2%), neuropathy (2%), syncope (2%), inner ear (2%)	30
100-600 mg thalidomide a day alone; 100-400 mg thalidomide a day and 20 mg/m ² dexamethasone (4 days, three cycles)	28; 40	10 (36%) 29 (72%)	Not recorded (for both groups)	Not recorded (for both groups)	Grade 3 (thalidomide; thalidomide and dexamethasone): constipation (68%; 55%), fatigue (39%; 55%), thrombosis (4%; 15%), infection (14%; 13%)	25
200 mg thalidomide a day and 40 mg/m ² dexamethasone (days 1-4, 9-12, 17-20); 40 mg/m ² dexamethasone (days 1-4, 9-12, 17-20)	103; 104	Not recorded (for both groups)	80%; 53%	Not recorded (for both groups)	Grade 3 (thalidomide and dexamethasone; dexamethasone): thrombosis (14%; 3%), neuropathy (5%; 3%), rash (4%; 0%), bradycardia (1%; 0%) Grade 4: not specified (31%; 15%)	31

Table 2: Thalidomide treatment in advanced and newly presenting multiple myeloma

symptoms), and extends stable disease. Several variations of this regimen exist, including use of intravenous cyclophosphamide, although oral CTD is a well-tolerated regimen that elicits excellent responses in VAD-refractory and relapsed myeloma (ie, complete and partial responses 57-79%),³⁹⁻⁴² and is now being tested in newly diagnosed patients in the MRC Myeloma IX trial.

Palumbo and colleagues⁴³ have studied the MPT combination of 4 mg/m² melphalan for 7 days every month, 40 mg/m² prednisone for 7 days every month, and 100 mg thalidomide a day in elderly patients who were ineligible for bone-marrow transplantation. Interim analysis of a prospective randomised trial comparing the efficacy and toxic effects of MPT with those of melphalan and prednisone was presented at the American Society of Hematology meeting in 2004.⁴³ The dose of thalidomide was reduced to 50% when grade 2 toxic effects occurred, was suspended for any grade 3 toxic effects, and the protocol was amended to include low-molecular-weight heparin prophylaxis. Responses for patients who received MPT were 26% complete response, 6% near-complete response, and 48% partial response, compared with 4% complete response and 44% partial response after melphalan and prednisone. Event-free survival at 26 months was 68% for MPT and 32% for melphalan and prednisone

($p < 0.001$); median overall survival has not been reached. The major adverse events of MPT compared with those of melphalan and prednisone were: deep vein thrombosis (19.3% vs 1.9%); grade 3-4 infections (13% vs 2%); grade 1-2 neurotoxic effects (36% vs 6%); and grade 3-4 haematological toxic effects (23% vs 27%).

Thalidomide is being investigated in the maintenance setting for its effect on the duration of response after high-dose chemotherapy and autologous stem-cell transplantation. The IFM 99-02 study⁴⁴ has 780 patients enrolled in IFM 99 who are without progressive disease 2 months after two autologous transplantations. Patients were randomly assigned to no maintenance treatment, maintenance with pamidronate alone, or maintenance treatment with thalidomide and pamidronate. In an interim analysis presented at the

	Number of patients	Reduction				Increase
		<25%	≥25 to <50%	≥50 to <75%	≥75 to <99%	≥25%
5 mg/day	3	0	2	1	0	0
10 mg/day	5	0	0	1	0	4
25 mg/day	3	1	2	0	0	0
50 mg/day	13	1	6	2	3	1
Subtotal	24	2 (8%)	10 (42%)	4 (17%)	3 (13%)	5 (21%)

Table 3: Maximum changes in paraprotein amounts after lenalidomide treatment by dose

American Society of Hematology meeting in 2004,⁴⁴ thalidomide with pamidronate increased progression-free survival compared with the other two groups ($p=0.002$); overall survival was similar in all three groups. Addition of thalidomide increased progression-free survival only in patients who had had at least a 90% response at randomisation ($p=0.05$), but not in those with a response lower than 90% ($p<0.10$).

Although thalidomide has shown activity in myeloma, it has several adverse side-effects that restrict its use in myeloma treatment, including somnolence, constipation, rash, fatigue, and neuropathy.⁴⁵ Neuropathy is a treatment-limiting disorder that affects 50–80% of patients who receive thalidomide, and could restrict long-term use of the drug.^{22,46} Less common side-effects include Stevens-Johnson syndrome, raised concentrations of liver enzymes, malaise, and peripheral oedema. Venous thromboembolism occurs in 1–3% of patients receiving thalidomide alone, and occurs more frequently when thalidomide is combined with dexamethasone (10–15%) or another cytotoxic drug (10–26%).⁴⁷ However, the increased risk of venous thromboembolism can be reduced by therapeutic anticoagulation.^{48,49}

In summary, because thalidomide-containing regimens are becoming increasingly used for relapsed patients, effectiveness must be weighed against side-effects, especially those of neuropathy and venous thromboembolism in thalidomide combinations. Other oral drugs that do not cause neuropathy might be preferable for use up front. Alternatively, pulsed dosing of effective thalidomide combinations such as CTD can produce substantial activity with fewer side-effects than those from continuous dosing.^{41–50}

Lenalidomide

The thalidomide derivative lenalidomide is the lead compound of the second-generation of immunomodulatory drugs initially developed as more potent inhibitors of tumour necrosis factor (TNF) α .^{26,51} Lenalidomide has immunomodulatory effects that include: growth arrest or apoptosis of drug-resistant myeloma cell lines; abrogation of myeloma-cell adhesion to bone-marrow stromal cells; and modulation of cytokines that promote the growth, survival, and drug resistance of myeloma cells.^{52,53} Lenalidomide is non-teratogenic in rabbits, and has a different clinical toxic-effect profile to that of thalidomide. Although such differences seem unexpected in view of the similar chemical structures of thalidomide and lenalidomide, the drugs have substantial differences on comparison of their three-dimensional crystal structures.

In phase I dose-escalation studies^{54,55} of patients with relapsed, refractory myeloma, myelosuppression was the dose-limiting toxic effect, and 25 mg a day was established as the maximum tolerated dose. In the first study,⁵⁴ 17 (71%) of 24 patients had at least a 25% reduction in

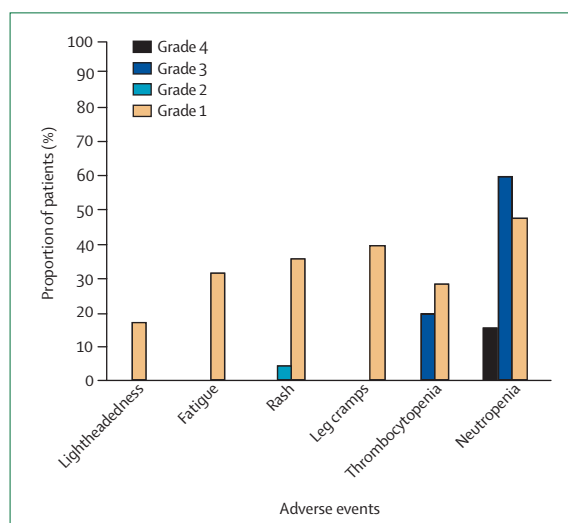


Figure 3: Common adverse events with lenalidomide in patients with relapsed, refractory multiple myeloma

paraprotein amounts, including 11 (46%) patients who had received previous therapy with thalidomide. Stable disease (<25% reduction in paraprotein) was noted for an additional two (8%) patients (table 3). These findings were corroborated by a second phase I study⁵⁵ in 15 patients with relapsed disease.

Phase II safety and efficacy studies^{55,56} have investigated lenalidomide in combination with dexamethasone in patients with relapsed, refractory myeloma⁵⁵ and newly diagnosed myeloma.⁵⁶ In a multicentre, randomised phase II study,⁵⁶ two different doses of lenalidomide (30 mg once daily or 15 mg twice daily for 3 weeks, followed by a 1-week rest) were compared in 101 patients with relapsed, refractory disease. Oral dexamethasone at a dose of 40 mg/day was added for 4 days every 2 weeks in patients who had progressive disease at 4 weeks of lenalidomide treatment and in patients with stable disease at 8 weeks or longer of treatment. 83 assessable patients showed an overall response of 38% (minor, partial, and complete response).⁵⁶ Of the 30 assessable patients who received dexamethasone in addition to lenalidomide, ten (33%) achieved at least some response. Grade 3 (or higher) thrombocytopenia and neutropenia occurred in 18% and 28% of patients, respectively.⁵⁶ Adverse events were more common in patients receiving lenalidomide 15 mg twice daily than in those receiving 30 mg once daily.

A second, phase II trial⁵⁷ is under way to assess the safety and efficacy of lenalidomide plus dexamethasone as initial therapy for newly diagnosed myeloma. In this study, patients received 25 mg lenalidomide a day on days 1–21 of a 28-day cycle and 40 mg dexamethasone a day on days 1–4, 9–12, and 17–20 of every cycle. Aspirin was given once daily as thrombosis prophylaxis. After 1–2 months of therapy, the total response was 83%.⁵⁷ At the preliminary analysis, no deep vein thrombosis and

no grade 4 or higher adverse events were recorded. Responses are still being assessed and will need to be confirmed when the final data are analysed. Other studies of myeloma, already in progress or soon to begin, include lenalidomide as initial therapy and as maintenance therapy after high-dose chemotherapy and autologous stem-cell transplantation.

The efficacy of 25 mg lenalidomide a day on days 1–21 of a 28-day cycle as seen in phase II studies was used as the basis for two large phase III studies (North American MM-009 and International MM-010) of patients with relapsed and refractory myeloma randomly assigned to lenalidomide and dexamethasone or to placebo and dexamethasone. Interim MM-009 trial data presented at the American Society of Clinical Oncology (ASCO) meeting in 2005 showed that the response (complete and partial) was significantly higher for the combination than for dexamethasone alone (62% vs 23%; $p < 0.001$). The time to progression for the combination treatment was highly significant and better than that for dexamethasone alone (15 months vs 5.1 months; $p < 0.0001$).⁵⁸

The most common major adverse event with lenalidomide is a predictable and reversible myelosuppression (figure 3).⁵⁴ Unlike thalidomide, lenalidomide has almost no sedative or constipating effects and only occasional neurotoxic side-effects. Lenalidomide combined with dexamethasone has a greater risk of venous thromboembolisms, and prophylactic anticoagulation is recommended. Lenalidomide is effective in patients refractory to thalidomide, and is another agent against multiple myeloma. In view of its low neurotoxic effects, use of lenalidomide could be preferable before thalidomide.

Inhibitors of RAS/RAF signalling

RAS mutations are often present in patients with myeloma. Consequently, the role of RAS/RAF/mitogen-activated protein kinase (MAPK) signalling in cytokine (ie, interleukin 6, VEGF, IGF-I)-induced proliferation of myeloma cells prompted several studies of the oral farnesyl-transferase inhibitors SCH-66336 and R115777 in relapsed, refractory disease.⁵⁹ The safety and response to R115777 in patients with relapsed, refractory myeloma was reported,⁵⁹ in which 43 patients received 300 mg R115777 twice a day for 3 weeks every 4 weeks. The most common toxic effect was fatigue, occurring in 66% of patients. Other toxic effects included diarrhoea, nausea, neuropathy, anaemia, and thrombocytopenia. Disease stabilisation took place in 64% of patients.⁶⁰ The activity of R115777 in combination with other cytotoxic drugs in myeloma is under investigation.

Histone deacetylase inhibitors

Histone acetyl transferases (HAT) and histone deacetylases (HDAC) function in chromatin assembly and transcriptional control. HAT activity opens chromatin by acetylating lysine tails of histones that

weaken the electrostatic interaction between DNA and histones. HDAC activity makes histones more positively charged, and close the chromatin. Evidence that HDAC inhibitors induce apoptosis in human myeloma cells *in vitro* has prompted investigation of these agents in relapsed, refractory myeloma.^{61–63} Preliminary findings were reported at the American Society of Hematology meeting in 2004 of an open-label, dose-escalation trial to investigate the safety and efficacy of the oral HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) in patients with advanced disease.⁶¹ In this study, SAHA (200 mg, 250 mg, and 300 mg twice a day) was given to eight patients with advanced myeloma for 5 consecutive days followed by 2 days of rest in 4-week cycles. Minor responses (25–50% reduction in serum paraprotein) were recorded in two patients, stable disease (<25% reduction) in two, and progressive disease in three. One patient treated with the 250-mg dose had grade 3 fatigue that was dose-limiting. Other treatment-related toxic effects included diarrhoea, indigestion, and dehydration. Clinical assessment continues to further define the safety and tolerability of SAHA, either alone or in combination with other drugs, in patients with advanced myeloma.⁶⁴

VEGF inhibitors

Inhibitors of VEGF have been identified as a potential therapy for myeloma, based on findings that VEGF secreted by myeloma cells and surrounding bone marrow stromal cells induces proliferation and migration of human myeloma cells.⁶⁵ PTK787/ZK222584 (PTK787) blocks VEGF-induced tyrosine phosphorylation of FLT1 (FMS-like tyrosine kinase 1, a VEGF receptor), activation of MEK (MAP-ERK) and MAPK, cell proliferation, and protein kinase C activation-dependent migration *in vitro*.^{65,66} These findings have provided the basis for a current phase I/II trial of oral PTK 787 in patients with relapsed disease.

P38 MAPK inhibitors

The production of various proinflammatory cytokines, including interleukin 1 β , interleukin 6, and TNF, all of which play a crucial part in myeloma, is mediated by P38 MAPK. Inhibition of P38 MAPK inhibits myeloma cell growth and survival in the bone-marrow milieu.⁶⁷ A phase I/II study is under way of the oral P38 MAPK inhibitor SCIO-469 as monotherapy, or in combination with bortezomib, in patients with relapsed, refractory myeloma.

Cyclin-dependent kinase (CDK) inhibitors

Cell-cycle progression is regulated by cyclins and their associated activating kinases, CDKs. Perturbations in cyclins and CDKs occur frequently in human tumours, leading to the development of CDK inhibitors for treatment. Seliciclib (CYC202 or R-roscovitine) is a small-molecule CDK inhibitor that promotes apoptosis

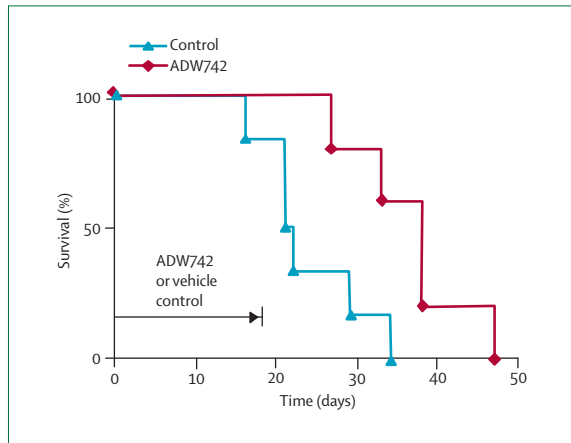


Figure 4: Kaplan-Meier survival curve of MM-1S orthografted mice receiving NVP-ADW742 (10 mg/kg given intraperitoneally twice daily) versus vehicle-treated control mice

Difference between regimens is $p=0.02$. Reproduced from with permission from ref 71.

of myeloma cells in vitro, inhibits RNA polymerase II-dependent transcription, and downregulates the anti-apoptotic factor MCL1.^{68,69} Seliciclib is currently in phase II clinical trials for the treatment of non-small cell lung cancer and B-cell haematological malignant diseases.

IGF-IR inhibitors

Signalling through IGF-IR promotes survival, anchorage-independent growth, oncogenic transformation in vitro, and tumour growth and metastasis in vivo. In myeloma, cells signalling through this receptor triggers polymerisation of F-actin, phosphorylation of focal adhesion kinase (p125^{FAK}) and paxillin, and enhances β 1 integrin interaction with these focal adhesion proteins.⁷⁰ NVP-ADW742 specifically inhibits IGF-IR kinase activity and has antimyeloma activity both in vitro and in vivo in a myeloma xenograft model (figure 4).⁷¹

FGFR3 inhibitors

A t(4:14) translocation is present in about 15% of patients with myeloma and results in overexpression of the tyrosine kinase activity of FGFR3. CHIR-258 is a potent inhibitor of FGFR3 kinase (inhibitory concentration 50% [IC₅₀] 5 nM) that stops phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 and induces a cytotoxic effect in primary myeloma cells from t(4:14) patients; therapeutic efficacy has been noted in a mouse xenograft of FGFR3 myeloma.⁷² A phase I trial in myeloma is under way.

Future role of oral treatments

Currently, most patients with myeloma given conventional chemotherapy have disease progression with the emergence of chemotherapy-resistant disease,

which accounts for the median survival of 3–4 years for symptomatic patients. The goal of therapy is to improve survival and extend duration of response while keeping toxic effects to a minimum. Oral drug treatments that show equivalent or better efficacy and tolerability than intravenous therapies are a welcome addition to the treatment currently available for multiple myeloma. Compounds such as thalidomide offer an alternative to cumbersome chemotherapy regimens and could improve patients' outcomes and quality of life. New oral therapies, such as lenalidomide, which are potent and have a manageable toxic-effect profile, could further improve treatment of relapsed, refractory, or newly diagnosed disease.

The next challenge will be to establish how and when these drugs can be used in the treatment of myeloma. Evidence from recent studies of thalidomide and lenalidomide in patients with myeloma suggest the need to reassess old treatment paradigms (figure 4).⁷¹ Although treatment is not warranted in asymptomatic patients, findings show that single-agent thalidomide has substantial activity in early-stage myeloma.²⁴ Thus, early treatment of asymptomatic patients with thalidomide could delay the progression to symptomatic disease. Thalidomide in combination with dexamethasone is more effective than is conventional combination therapy as salvage treatment for refractory, relapsed disease,³² and as an effective induction therapy for patients with newly diagnosed myeloma, including before autologous bone-marrow transplantation.^{31,37} These results have prompted a shift in the approach to myeloma treatment, and oral therapy could now be judged as first-line therapy over that of conventional combinational chemotherapy and single-dose dexamethasone in patients with newly diagnosed disease, and as salvage therapy for relapsed, refractory disease, in view of its equivalency and greater simplicity.

Another important new advance has been the proteasome inhibitor bortezomib.⁷³ Although it is effective clinically, this drug needs intravenous pushes with all its effectant disadvantages. Studies of bortezomib in vitro and in vivo have suggested that it can combine synergistically with the new drugs discussed above.^{74,75} The development of orally bioavailable forms of bortezomib is under way and would enhance greatly current treatment options for myeloma. Other promising compounds in intravenous trials are the inhibitors of heat shock protein 90 (HSP90). HSP90 is a molecular chaperone, of which the precise function is unclear. However, HSP90 associates with steroid hormone receptors, tyrosine kinases such as FGFR3 and eukaryotic initiation factor (eIF) 2 α kinase, and oncoproteins.⁷⁶ 17-AAG (17-[Allylamino]-17-demethoxygeldanamycin) is a rifabutin antibiotic that inhibits HSP90, and has shown activity as an intravenous drug in a phase I myeloma trial;^{77,78} several other orally bioavailable HSP90

Search strategy and selection criteria

We used PubMed (1996 to August, 2005) and meeting abstracts (American Society of Clinical Oncology, 2003–05, American Society of Hematology, 2003–04, and European Hematological Association, 2003–05) as the sources of the material covered. Keywords searched were: “myeloma”, “oral therapy”, “novel therapy”, “orally bioavailable”, “chemotherapy”, “immunomodulatory”, “mitogen activated protein kinase”, “angiogenesis”, “histone deacetylase”, “cyclin dependent kinase”, “tyrosine kinase”, “farnesyltransferase”, “HSP 90”, “FGF”, “IGF”, “Ras”, and “RaK”. We have included all relevant preclinical and clinical studies of oral therapies in multiple myeloma. We have tried to give due representation to therapeutic substances according to the volume of published work.

inhibitors are under preclinical investigation. Therefore, HSP90 inhibitors could have a biological rationale for combining with other new substances, including bortezomib and lenolidamide.

Recent advances in the understanding of myeloma pathogenesis have led to the development of several new drugs that specifically target myeloma-cell growth and survival. Of these compounds, oral therapies such as thalidomide and lenalidomide are promising, either alone or in combination with dexamethasone, in both refractory and newly diagnosed disease. Thus, oral treatments represent a new treatment paradigm for multiple myeloma and provide alternatives to intravenous drugs at various stages of disease course or treatment. Over the next decade, the challenge will be to define the role of oral drug combinations with each other or with conventional chemotherapy in resistant or early-stage disease to improve patients' outcomes.

Conflicts of interest

We declare no conflicts of interest.

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