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LENALIDOMIDE: THE OPTIMAL CHOICE IN NEWLY DIAGNOSED MULTIPLE MYELOMA

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Various options exist for the treatment of multiple myeloma (MM). Patients with relapsed or refractory MM, for example, show good responses to treatment with a combination of lenalidomide and dexamethasone.^{1,2} Patients with newly diagnosed MM who can not undergo stem cell transplantation (SCT) commonly undergo initial treatment with melphalan plus prednisone, and patients who can undergo SCT may receive induction therapy consisting of vincristine, doxorubicin, and dexamethasone. Limitations of these regimens, however, including adverse events and poor tolerability and response rates, have led to the development of new agents, which are undergoing clinical trials. In trials of patients with newly diagnosed MM, lenalidomide plus dexamethasone has shown promising results,³⁻⁵ with lenalidomide plus low-dose dexamethasone producing a higher 2-year survival rate and better safety profile than lenalidomide plus high-dose dexamethasone (ECOG-E4A03 trial).⁵ Newly diagnosed MM patients have also shown high response rates and manageable adverse events after receiving lenalidomide, melphalan, and prednisone (RMP regimen).⁶ Investigational regimens for primary MM include clarithromycin, lenalidomide, and dexamethasone (BiRD regimen). Phase II results indicate that this regimen is highly effective (overall response rate 95%; complete or near-complete response rate 38%); data also suggest that prolonged use of BiRD may be a feasible option for patients who are not candidates for peripheral-blood SCT.⁷ The feasibility of long-term lenalidomide treatment as maintenance therapy after autologous SCT is being evaluated in the CALGB-100104 and IFM 2005-02 trials, and the use of lenalidomide in newly diagnosed patients older than 65 years who are not SCT candidates is being evaluated in two pivotal clinical trials, MM-015 and MM-020. In summary, clinical trials indicate that lenalidomide (alone or in combination with other agents) shows promising efficacy and safety in patients with newly diagnosed MM and as maintenance therapy for MM. Time to progression and its correlation with other survival benefits support the long-term use of lenalidomide.

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CHOOSING THE BEST STRATEGY IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Several new options exist, including thalidomide and bortezomib, for the treatment of relapsed or refractory multiple myeloma (MM). Although these treatments have significantly improved outcomes, relapse and treatment resistance are almost inevitable. Innovative treatments (such as lenalidomide) that induce durable responses and prolong time to progression (TTP) and time to next therapy are needed.

Two phase III trials (MM-009 and MM-010) evaluated the safety and efficacy of lenalidomide plus dexamethasone (Len + Dex) versus high-dose dexamethasone (Dex) in patients with relapsed or refractory MM.^{1,2} The main adverse events – neutropenia, thrombocytopenia, and venous thromboembolism – were more frequent with Len + Dex than with Dex,^{1,2} most were manageable with lenalidomide dose reduction, treatment interruption, and prophylaxis.¹⁻³ Len + Dex was superior to Dex in terms of response rates, TTP, and overall survival in both trials. Median TTP with Len + Dex was 11.1 months in MM-009 and 11.3 months in MM-010; and with Dex alone, 4.7 months (both trials). Len + Dex has induced longer TTP and overall survival in complete responders than in partial responders.⁴ Superior efficacy of Len + Dex over Dex alone is observed regardless of prior stem cell transplantation⁵ or thalidomide exposure,^{1,2} thalidomide resistance,⁶ poor prognostic features [e.g. renal impairment⁷ or del(13) or t(4;14)],⁸ or the number of previous therapies.^{1,2,9} A subgroup analysis confirmed that Len + Dex is more effective than Dex at first relapse and beyond.^{1,2} In patients with 1 prior therapy, a response occurred in approximately 65% of those receiving Len + Dex and in approximately 26% of those receiving Dex. In patients with more than 1 prior therapy, a response occurred in approximately 58% of those receiving Len + Dex and in approximately 20% of those receiving Dex. Median TTP was significantly longer in patients who received Len + Dex than in those who received Dex alone, irrespective of the number of prior treatments.⁹ TTP was longer when Len + Dex was used at first relapse (TTP 15.5 months) than when used later (TTP 10.2 months). Several trials in relapsed or refractory MM are exploring combinations of lenalidomide with liposomal doxorubicin, vincristine, and dexamethasone (DVR);¹⁰ dexamethasone and adriamycin (RAD);¹¹ dexamethasone, adriamycin, and cyclophosphamide (RCD);¹² and bortezomib.¹³ The benefits of “triple therapies” (i.e. a combination of 3 of an immunomodulatory agent, a proteasome inhibitor, conventional chemotherapy, and corticosteroids) for relapsed and persistent disease are being explored.

In conclusion, compared with Dex alone, Len + Dex raises response rates and prolongs TTP and overall survival in patients with relapsed or refractory MM,

regardless of the type and number of prior therapies. These findings illustrate the promise of lenalidomide in combination with other active agents for treatment during early and later relapse of MM.

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LOOKING FORWARD IN NON-HODGKIN LYMPHOMA: LENALIDOMIDE TREATMENT

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Patients with indolent non-Hodgkin lymphoma (NHL) have a median survival of 10 years, but the disease is rarely cured. Recent phase II data demonstrated the efficacy and safety of oral lenalidomide monotherapy in relapsed or refractory indolent NHL (NHL-001), with an overall response rate (ORR) of 26%, which included 2 complete responses (CRs), 1 complete response unconfirmed (CRu), and 8 partial responses (PRs). Progression-free survival (PFS) was 4.6 months for all patients and > 7.7 months for patients with a response (ongoing); the most common grade 4 adverse event was neutropenia (14%), and the most common grade 3 adverse events were neutropenia (21%) and thrombocytopenia (12%).¹

The main cause of death in aggressive NHL is relapse or non-response to initial therapy. In a phase II multi-centre trial evaluating the safety and efficacy of lenalidomide in patients with relapsed or refractory aggressive NHL (NHL-002), lenalidomide had an ORR of 34%, including 5 CRus and 9 PRs. PFS is currently more than 239 days (range > 191 to > 373) in patients with a CRu and more than 160 days (range > 54 to > 251) in patients with a PR. The most common grade 4 adverse events were neutropenia (8.2%) and thrombocytopenia (8.2%), and the most common grade 3 adverse events were neutropenia (22%), leukopenia (14%), and thrombocytopenia (12%).² In a subgroup analysis of the NHL-002 trial investigating the impact of prior stem cell transplantation (SCT), 50% of patients exhibited an objective response (1 CRu and 6 PRs), and 4 (67%) of 6 patients who had SCT as their last treatment before receiving lenalidomide had a response. PFS was 4.5 months and ongoing.³ Mantle cell lymphoma (MCL) is a distinct type of aggressive NHL characterized by being incurable and showing a low rate of response to conventional chemotherapy agents. Recently, a subgroup analysis of the NHL-002 trial and an independent trial at the M.D. Anderson Cancer Center demonstrated the promising activity of lenalidomide, alone or in combination with rituximab, in patients with relapsed or refractory MCL. ORRs were 53% for lenalidomide alone and 70% for lenalidomide plus rituximab.^{4,5}

In conclusion, oral lenalidomide monotherapy is active and has manageable side-effects in patients with relapsed or refractory, indolent or aggressive NHL.

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TREATMENT OF RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKAEMIA

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Lenalidomide is a thalidomide analogue with clinical activity in del(5q) myelodysplastic syndromes and multiple myeloma. Its precise mechanism of action is not known, but it is likely to be different from that of classic chemotherapeutic agents. In addition, different mechanisms of action may be relevant, depending on the underlying disease. In del(5q) myelodysplastic syndromes there is evidence that lenalidomide directly inhibits the growth of del(5q)-positive erythroid progenitors and upregulates the tumour suppressor gene *SPARC* and the pleiotropic gene encoding activin A.¹ In contrast, in multiple myeloma, lenalidomide increases the rate of apoptosis of neoplastic plasma cells, inhibits cell adhesion, and induces changes in the bone marrow microenvironment.² The mechanism of action of lenalidomide in chronic lymphocytic leukaemia (CLL) is still under investigation. Possible activities include activation of T and NK cells; downregulation of pro-survival cytokines such as TNF- α , VEGF, and IL-6; and interference with the microenvironment and the CLL-stroma interaction.³ Two phase II trials investigating lenalidomide in relapsed or refractory CLL have been completed.^{4,5} Lenalidomide was given orally according to different schedules in the two studies. In that reported by Chanan-Khan and colleagues, patients received lenalidomide 25 mg daily, 3 weeks on, 1 week off.⁴ Patients in our study received lenalidomide daily without interruption.⁵ The starting dose was 10 mg and could be increased up to 25 mg/day by monthly increments of 5 mg/day. Even in patients receiving up to 25 mg/day, the median dose was 10 mg/day. Results were reported on 29 response-evaluable patients by Chanan-Khan and colleagues⁴ and on 44 patients in our study.⁵ Both trials included heavily pretreated patients and high proportions of patients with unfavourable prognostic factors (e.g. elevated β_2 -microglobulin, genomic abnormalities, unmutated immunoglobulin heavy-chain genes) and patients with fludarabine-refractory disease.^{6,7} Both studies indicated that lenalidomide has activity in relapsed disease: overall response rates were 47% and 32%, and complete response rates were 9% and 7% in the Chanan-Khan study and our study, respectively. Responses appear durable with continuation of therapy. Myelosuppression was the main side-effect of lenalidomide treatment: severe neutropenia was observed in 70% of the patients in the Chanan-Khan study and in 39% of the patients in our study. Grade 3 or 4 tumour-flare reaction was reported in both studies: its incidence was higher (8%) with the starting dose of 25 mg than with the starting dose of 10 mg (1%).

Ongoing studies are assessing the activity of lenalidomide as initial therapy for elderly patients with CLL and in combination with other agents, such as fludarabine and rituximab, in patients with relapsed and refractory disease.⁸

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