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Thalidomide therapy induces response in relapsed mantle cell lymphoma

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Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma that cannot be cured despite aggressive therapy, including autologous stem cell transplantation. Thalidomide is an immunomodulatory drug with numerous properties that has proven effective in relapsed multiple myeloma and, to a lesser extent, in other hematological diseases, such as myelodysplastic syndromes and myeloproliferative disorders. We report two cases of relapsed refractory MCL successfully treated with thalidomide.

The first patient is a 70-year-old man, who presented in 1995 with stage IV MCL. He was treated according to the current protocol at our institution, as reported elsewhere.[1] He received CHOP x four cycles with only a partial response (PR), followed by high-dose cytarabine-based chemotherapy (DHAP), and consolidation with an autologous stem cell transplant utilizing total body irradiation (TBI), melphalan, and cytarabine as the preparative regimen. A complete response (CR) was obtained. The patient relapsed 40 months later, presenting with diffuse peripheral and abdominal lymphadenopathy, splenomegaly, bone marrow and peripheral blood involvement, and a lactate dehydrogenase (LDH) level twice the normal. As salvage chemotherapy, the patient received concurrent cytarabine (2 g/m^2/12 h, days 1–3) and etoposide (200 mg/m^2/day, days 1–3). After a transient response, the patient progressed 3 weeks after the third cycle. The patient next received two cycles of concurrent fludarabine (30 mg/m^2/day, days 1–3) and cyclophosphamide (300 mg/m^2/day, days 1–3), and obtained PR. Treatment was complicated by persistent grade 4 pancytopenia (ANC $<0.1 \times 10^9$/l) and infection. As a consequence, the patient declined further chemotherapy. After 4 months, when the patient's peripheral lymphadenopathy increased, he received a 4-week course of rituximab (375 mg/m^2 per week) without any response. In June 2001, the patient developed worsening pancytopenia and compressive iliac lymphadenopathy and started thalidomide at 200 mg/day, increasing by 100 mg/day every 2 weeks, up to 500 mg/day. Hematopoiesis and lymphadenopathy progressively improved, with the patient becoming transfusion independent within 2 months of beginning thalidomide. By the 4th month, the hemoglobin and platelet levels had reached 12 g/dl and 176×10^9/l, respectively, with a complete disappearance of peripheral blood atypical lymphocytes and a 50% reduction in the size of the lymphadenopathy. Over the next year, the patient maintained his response on 300 mg/day of thalidomide. Although the patient was tolerating the thalidomide, the dose was decreased to 200 mg/day for 2 weeks each month, to decrease the risk of chronic thalidomide side effects. After 4 months (September 2002), the patient's disease progressed, with reappearance of the pancytopenia and increased lymphadenopathy. A bone marrow examination was not performed. Thalidomide was increased to 200 mg each day in combination with three courses of monthly dexamethasone (40 mg/day x 4 days), reachieving a partial response. At 19 months since first starting thalidomide, the patient remains alive and with a good partial response.

The second patient is a 56-year-old man, who presented with stage IV MCL, and initially achieved a CR after receiving three cycles of CHOP, followed by three cycles of DHAP in combination with rituximab, and an autologous stem cell transplant utilizing TBI, melphalan, and cytarabine as consolidation. After 2 years (May 2002), the patient relapsed with bone marrow involvement, splenomegaly, an elevated LDH (600 IU/L), and a poor performance status (KPS = 3). He was started on thalidomide 100 mg/day plus dexamethasone (40 mg/day x 4 days). After 1 month, the patient demonstrated a significant decrease in splenomegaly and the LDH level, but remained pancytopenic. The dose of thalidomide was not increased because of side effects (constipation, fatigue, and paresthesia) and the dexamethasone was stopped. Over the next 5 months, while taking only thalidomide 100 mg/day, the patient demonstrated progressive improvement of his disease, with resolution of the splenomegaly, normalization of the LDH and hemoglobin levels, and significant improvement of his neutrophil and platelet counts (1.0 and 86×10^9/l, respectively). At last follow-up (March 2003), the patient maintains his response, taking thalidomide 100 mg/day without any severe toxicity.

Since the first and subsequent reports of its efficacy in multiple myeloma,[2–4] there has been a growing interest in thalidomide as an anticancer therapy. The precise mechanisms responsible for thalidomide's antitumor effect remain unknown. Thalidomide may act directly on tumor cells to induce apoptosis or cell cycle arrest,[5] or indirectly, by acting to inhibit angiogenesis,[6] alter immune cell cytokine secretion,[7] enhance T cell,[8] natural killer cell,[7] and dendritic cell activity,[9] and inhibit NF-κB activity.[10] These two cases represent the first two reports of the therapeutic potential of thalidomide in refractory MCL. Based on these encouraging preliminary results, and the immediate need for improved therapy for the treatment of MCL, prospective phase II trials involving larger groups of patients are warranted. *In* vitro studies are underway to delineate the mechanism of action of thalidomide in MCL.

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AML with t(8;21) and trisomy 4: possible involvement of *c-kit*?

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TO THE EDITOR

Nishii *et al*[1] have recently described a minor subset of acute myeloid leukemia (AML) patients with t(8;21) and trisomy 4, who had a relatively poor prognosis when compared to t(8;21) AML patients with or without other cytogenetic abnormalities. A review of the literature suggests a possible mechanism for this poor prognosis. Current theory regarding the pathogenesis of AML, especially in those patients with either a t(8;21)(q22;q22) or inv(16)(p13q22) abnormality, has postulated the cooperativity of core-binding factor (CBF) gene rearrangements (AML *1-€TO* and *CBFB-MYH11*, respectively) with mutations in those genes encoding receptor tyrosine kinases (eg FLT3, KIT).' In particular, mutations of the c-kit gene, located at chromosome 4q11–q12, have been detected in a significant proportion of patients with CBF-AML[3] and also in two patients with t(8;21) and trisomy 4.[4] In one of these latter patients, the trisomy 4 lead to duplication and thus increased dosage of the mutated c-kit allele,[5] suggesting an additional mechanism of leukemogenesis. This observation is supported by evidence of amplification of a c-kit mutation in the t(8;21) and trisomy four-positive cell line Kasumi-1.[6] Further investigation is therefore warranted to determine the presence of c-kit mutations in the three t(8;21) AML patients with trisomy 4 described by Nishii etal,' as the most common activating mutation of c-kit has been show to confer drug resistance,[7] which could be partly responsible for the relatively poor prognosis. If mutations are present, these patients may be eligible for additional treatment with novel therapies that inhibit KIT tyrosine kinase activity.'

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Reply to SE Langabeer *et al*

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TO THE EDITOR

Dr. Langabeer and his colleagues made several interesting suggestions in discussing our recent paper.' Our work showed that t(8;21) acute myeloid leukemia (AML) with trisomy 4 had different morphology, phenotype, and clinical outcome when compared to t(8;21) AML with or without other chromosomal abnormalities, especially t(8;21) AML plus trisomy 4 having a poor prognosis. Dr. Langabeer *et al,* speculate that the presence of c-kit mutation in the t(8;21) AML patients with trisomy 4 may have caused these events. It had been reported that c-kit mutations were more frequently observed in core binding factor leukemia.[2,3] Among these c-kit mutations, mutation of codon 816 (most commonly Asp816Val) of the c-kit caused constitutive activation of the KIT kinase[4,5] and had been shown to confer drug resistance.[6,7] Therefore, we examined for c-kit mutation in a t(8;21) AML with trisomy 4 sample among those reported by Nishii *et al,*[1] only one sample was available for analysis. Mutation screening was targeted on exon 17 at codon 816 (amino acid 2468) of c-kit. cDNA was amplified using reverse transcription-polymerase chain reaction (RT-PCR) method and amino-acid sequence was investigated as described previously.[8,9] As shown in Figure 1, the presence of the Asp816Val mutation was detected in leukemic cells from this sample. Beghini et *al*[10,11] also reported the mutation of codon 816 of c-kit gene in two cases of t(8;21) AML with trisomy 4. These observations led us to speculate that an activating mutation of c-kit may be associated with t(8;21) AML with trisomy 4, perhaps this additional aberration could have caused the poor prognosis. To confirm the relationship between

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