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Lenalidomide: an emerging option in chronic lymphocytic leukemia

Lenalidomide is a thalidomide-derivative that has shown clinical activity in multiple myeloma, myelodysplastic syndrome (del5q syndrome) and non-Hodgkin's lymphomas. It belongs to a class of agents called immunomodulating drugs (IMiDs). In comparison to thalidomide, it is a more potent inhibitor of tumor necrosis factor alpha (TNF-α), while retaining some of its anti-angiogenic properties.

Our group became interested in evaluating the therapeutic potential of lenalidomide in chronic lymphocytic leukemia (CLL) while searching for TNF-α and VEGF inhibitors. The rationale for targeting TNF-α and VEGF in CLL is based on our observation that patients with CLL have higher levels of TNF-α and VEGF-R2 than normal subjects and that high levels of these cytokines are associated with more aggressive disease and an inferior outcome.[1,2]

We initially investigated the clinical activity of lenalidomide in patients with relapsed/refractory CLL. Lenalidomide was given at the starting dose of 10 mg daily without interruption (this regimen was modeled on the experience with this agent in myelodysplastic syndrome) with monthly dose escalation up to 25 mg/day.

Forty-four patients were enrolled in this study. All had advanced disease and were heavily pre-treated with a median number of 5 prior treatments. A significant proportion of patients in this trial had unfavorable prognostic features: an elevated median b-2-M (4.3 mg/dL), unmutated Ig_{VH} genes (66% of patients), poor prognostic genomic abnormalities (del11q in 41%; del17p in 18%), refractoriness to fludarabine (24% of patients). Treatment with lenalidomide was associated with an overall response rate of 32%, with 7% of the patients achieving a complete response (Table 1). The most common toxicity in this population with relapsed/refractory disease was myelosuppression.[3] Our results confirmed the finding of Chanan-Khan and collaborators who used different regimen of lenalidomide (intermittent dosing, 25 mg daily 3 weeks on; 1 week off) in a similar patient population of patients with recurrent CLL.[4]

In order to further explore our rationale of using lenalidomide as inhibitor of inflammatory cytokines and angiogenesis, we measured circulating plasma levels of inflammatory cytokines and angiogenic factors and measured bone marrow neovascularization in a proportion of the patients receiving treatment in this study. Our correlative studies did not demonstrate an inhibition of TNF-α. We instead noticed a transient increase in TNF-α receptor-1 lev-

els during the first week of therapy. Similarly, no changes in bone marrow neo-angiogenesis were detected. On the other hand, we found a statistically significant change in the plasma levels of FGS-basic, interleukin-10 and interleukin-2, and also a sharp increase in interleukin-6, interleukin-10, interleukin-2 receptor on day 7, followed by a their decline with continuation of therapy. We also observed that the number of circulating $CD3^+$ T-cells remained stable during treatment in this group of patients, and they represented the majority population of circulating lymphocytes in responding patients (Figure 1).[3]

Encouraged by the activity of lenalidomide in this advanced patient group, we further explored its activity as initial therapy of elderly patients with CLL. Elderly patients often experience prolonged myelosuppression with chemoimmunotherapy and chemotherapy combinations and have difficulty in completing the planned course of therapy and therefore represent a patient population that could potentially benefit from a different approach to treatment.[5] We also sought an advantage in using an oral agent in this large group of patients, and we wanted to explore the activity lenalidomide in an untreated population. A phase II clinical study of lenalidomide as initial treatment of patients with CLL, age 65 or older is now ongoing at our institution. The patients receive treatment with lenalidomide daily with a starting dose of 5 mg and slow dose escalation. Patients are treated with allopurinol for tumor lysis syndrome prophylaxis for the first two weeks and they have their blood counts and laboratory metabolic profile monitored at least weekly during the initial phase of treatment. The results of this study were reported at the 2008 American Society of Hematology meeting and have been recently updated. The median age of the patients enrolled in this study is 72 years. As expected in a population of patients with CLL requiring treatment, median

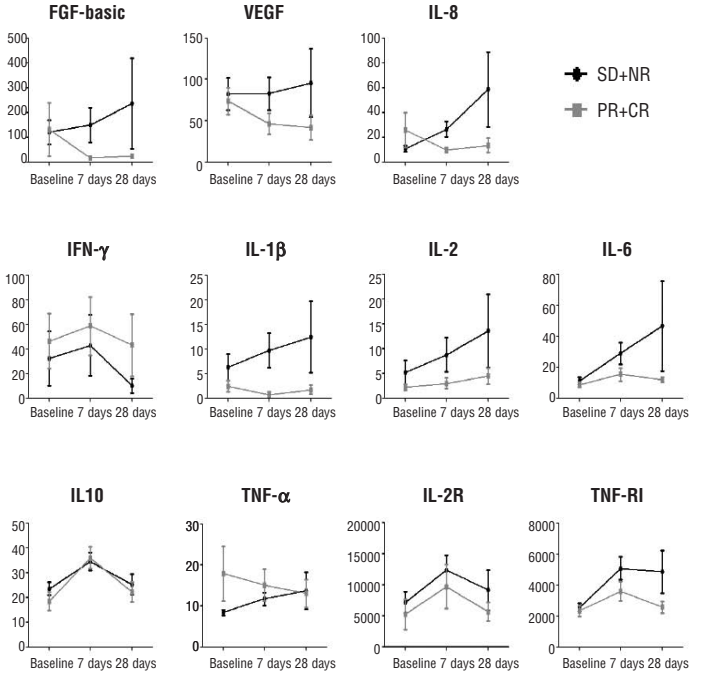

Figure 1. Peripheral blood was collected from patients receiving lenalidomide therapy at baseline and after 7 days and 28 days of treatment. Plasma samples from patients with stable disease or no response (SD + NR, gray lines) and partial response or complete response (PR + CR, black lines) were analyzed for the angiogenic factors FGF-basic, VEG, and IL-8, the inflammatory cytokines IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α, and the soluble cytokine receptors IL-2R and TNF-RI. Longitudinal analysis of SD + NR showed significant changes over time in IL-6, IL-10. IL-2R, TNF-RI. PR + CR show significant changes over time in FGF-basic, IL-10 and IL-2R. The change in VEGF concentrations was not statistically significant for either group. Plasma concentrations are reported in pg/mL.

Table 1. Responses to treatment.

Response	*No. of Patients*	*%*
Overall response	14	32
CR	3	7
Nodular PR	1	2
PR	10	23
Stable disease	11	25
Progressive disease	19	43

β2M at baseline was elevated (4.5 mg/dL), 65% of them had unmutated IgV_H genes, 67% expressed ZAP-70 and 30% carried unfavorable genomic abnormalities. At the most recent update 45 patients have completed 3 cycles of therapy with an overall response rate of 44% and a stable disease rate of 47%. Forty patients have completed 9 cycles of therapy, with an overall response rate of 55% (including one complete remission) and a stable disease rate of 12%. Twelve patients had the potential to reach 15 cycles of therapy, and the overall response rate in this group is 67% with a complete response rate of 8% suggesting that quality of response improves with continuation of therapy. The most significant toxicity observed in this population was myelosuppression, particularly neutropenia. Tumor flare reaction (a finding observed by other investigators as well as by us in patient with CLL receiving lenalidomide treatment) was observed, with an occurence rate of 46%. The tumor flare reaction was mild in the majority of patients [grade 3 in one patient (2%), grade 1 or 2 in the remaining cases]. We monitored changes in circulating lymphocytes during treatment and noticed an increase in the proportion of circulating T-cells that was accompanied a decrease in absolute lymphocyte count.[6] In patients receiving therapy for 15 months or longer, T-cells represented 70% of the circulating lymphocytes. In patients receiving treatment in this study, T-cells regained immune reactivity with increased production of pro-inflammatory IFN-γ. Circulating T-regulatory cells were measured in a subgroup of patients. Even when their number increased with therapy, the induced IL-10 production was decreased.[7] These most recent findings point toward an immunomodulatory effect of lenalidomide in patients with CLL and are in agreement with data reported by other groups in multiple myeloma, as well as with findings from other investigators.[8,9]

We are currently exploring the activity of lenalidomide in combination with rituximab in patients with relapsed/refractory disease, and we are evaluating lenalidomide as a strategy to eliminate residual disease after chemoimmunotherapy.

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