**Lenalidomide: what is the right dose in CLL?**

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Ferrajoli and colleagues present the results of a phase 2 study in which lenalidomide was administered by continuous daily dosing to 44 patients with relapsed CLL. Clinical activity (ORR 32%, CR 7%) was observed, and responses were seen in patients with poor-risk cytogenetic abnormalities and unmutated IgVH. However, the mechanism(s) of action and the optimal dosing schedule of lenalidomide remain undefined.

The immunomodulating drug lenalidomide is approved for treatment of multiple myeloma (MM) and 5q- myelodysplastic syndrome (MDS). However, its mechanism of action remains unclear and may be disease specific. The maximal tolerated dose was 25 mg daily in MM, but 10 mg daily was as effective as, and caused less hematologic toxicity than, 25 mg daily in MDS. Thus, lenalidomide’s tolerability and optimal dose, like its mechanism of action, may be disease specific.

Chanan-Khan and colleagues administered lenalidomide at a dose of 25 mg daily on days 1 to 21 every 28 days to 45 patients with relapsed chronic lymphocytic leukemia (CLL). Lenalidomide was active (overall response rate [ORR] 47%, complete remission [CR] 9%), although hematologic toxicity at grades 3 and 4 was significant, and 2 patients developed tumor lysis syndrome. Furthermore, 58% of patients experienced a unique tumor flare reaction, occurring within 24 hours of the first dose and lasting a median of 14 days, which was not observed in MM or MDS.

In this issue of Blood, Ferrajoli and colleagues present the results of a phase 2 study in which lenalidomide was administered at 10 mg per day by continuous daily dosing to 44 patients with relapsed CLL. The dose could be escalated 5 mg every 28 days up to 25 mg daily, but significant hematologic toxicity resulted in 10 mg being the median delivered dose. The authors observed an ORR of 32% (CR 7%), with activity apparent in patients with high-risk cytogenetic abnormalities (ORR 31%) and unmutated IgVH (ORR 25%), although 6 to 9 months were needed to achieve optimal response. In contrast to agents such as fludarabine and alemtuzumab, lenalidomide caused no reduction in T-cell counts, although 1 patient died of pneumonia and 1 patient died of mucormycosis during cycle 1, perhaps due to prior immunosuppression.

Thirteen patients (30%) developed tumor flare reactions, which were treated with a 6-day solumedrol pack; lymph node size greater than 5 cm was the only identified risk factor. Clinical response did not depend upon development of tumor flare. In contrast to its ability to reduce IL-6 production in MM, which may be critical to its activity in that disease, lenalidomide did not reduce IL-6 levels in responding CLL patients, and actually induced a dramatic increase in IL-6 in nonresponders. No significant change in TNF-α was observed with therapy, although responders had a mean baseline TNF-α level twice that of nonresponders. The correlative study discussed by Ferrajoli et al suggests an immunostimulatory effect, although lenalidomide’s mechanism of action in CLL remains unclear.

The article by Ferrajoli and colleagues indicates that continuous low-dose lenalidomide may be as effective as an interrupted schedule using higher doses. At 5 mg daily, 3 of 11 patients responded, and a CR was observed at 10 mg daily. However, this study also illustrates the toxicity of lenalidomide in heavily treated, relapsed CLL patients. Despite a median dose of 10 mg daily, significant hematologic toxicity was observed, and 30% of patients developed tumor flare reactions. Although lenalidomide appears to exert an immunostimulatory effect, its mechanism of action in CLL remains unclear and requires further investigation. Although lenalidomide is clearly active in CLL, more clinical studies are needed to define the optimal dosing schedule and confirm the safety of lenalidomide in treating this malignancy.

Conflict-of-interest disclosure: The author has served on advisory boards for Celgene, which produces and licenses lenalidomide (Revlimid).

**REFERENCES**


Comment on Hinrichs et al, page 5326

**IL-21 priming enhances T-cell immunotherapy**

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In this issue of Blood, Hinrichs and colleagues report that priming T cells with interleukin (IL)–21 can potently enhance their antitumor effects following adoptive transfer, whereas priming T cells with IL–2 impairs their antitumor function.

Over the past 2 decades, IL–2 has been commonly used to generate effector T cells for the adoptive immunotherapy of cancer. Transfer of IL–2–activated, tumor-specific T cells has led to some remarkable cases of tumor regression in patients with metastatic melanoma. However, the use of IL–2 appears to be a double-edged sword. Although IL–2 can induce activation and proliferation of CD8+ T cells, it can also induce activation–induced cell death and is important for the development of T regulatory cells.
Recent studies have revealed that the differentiation state of CD8\(^+\) T cells following transfer can affect their ability to mediate tumor rejection. Indeed, studies in patients have shown that persistence of transferred T cells and subsequent antitumor responses correlate well with cells being in a early state of effector T-cell differentiation.\(^3\) These results raise the intriguing possibility that the use of cytokines other than IL-2 that can repress differentiation of CD8\(^+\) T cells into cytolytic effector cells may lead to more profound antitumor responses.

In their article, Hinrichs and colleagues show that IL-2 and IL-21, which share the common cytokine receptor \(\gamma\)-chain, mediate opposing effects on antigen-induced CD8\(^+\) T-cell differentiation. Priming naive CD8\(^+\) T cells with IL-2 or IL-15 promotes their cytolytic effector function but impairs their antitumor capability in vivo. In contrast, priming naive CD8\(^+\) T cells with IL-21 suppresses their cytolytic effector function but enhances their ability to mediate tumor regression in vivo.

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In conclusion, the above findings have important implications for developing more effective immunotherapies for cancer. However, several important questions remain. Can IL-21–primed T cells mediate enhanced tumor regression in other models, particularly against metastatic disease? Can IL-21–primed T cells generate an effective antitumor response against secondary challenge? It is becoming increasingly clear that understanding how different cytokines program CD8\(^+\) T cells will lead to maximizing the enormous potential of adoptively transferred T cells for cancer immunotherapy.

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