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**Lenalidomide in AML: Del(5q) or who?**

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Outcomes for older adults diagnosed with acute myeloid leukemia (AML) continue to be poor, especially for patients with therapy-related AML or AML arising from an antecedent hematologic disorder such as a myelodysplastic syndrome (MDS). Even the subset of older patients deemed fit enough to receive intensive induction chemotherapy have only a modest (40%-50%) likelihood of achieving complete remission (CR), and the average duration of such remissions is less than a year; reported 5-year survival rates for patients diagnosed with AML after age 70 are as low as 5%.

This dismal outlook has prompted investigators to conduct clinical trials exploring a wide range of alternative approaches, either instead of or in combination with induction chemotherapy. Such approaches include hypomethylating agents and deacetylase inhibitors that modify gene expression by epigenetic mechanisms, newer antimetabolites, apoptosis-promoting compounds, immunostimulatory and immunomodulatory agents, inhibitors of multidrug resistance, drugs intended to disrupt the marrow microenvironment or leukemic stem cell niche, and kinase inhibitors.

The overall goal of these trials has been to find therapies that are well tolerated and also prolong survival beyond what would be expected with supportive care alone or the standard anthracycline/cytarabine chemotherapy combinations in widespread use since the 1970s. Clinical benefit from the immunomodulatory agent lenalidomide in patients with lower-risk MDS associated with deletion of the long

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Proposed molecular and cellular targets of lenalidomide with potential relevance to human neoplasia. Lenalidomide’s biologic effects include alteration of tumor cells’ progression through the cell cycle, changes in the marrow microenvironment including disruption of the stem cell niche and inhibition of angiogenesis, variation in levels of inflammatory mediators and cytokines, and modification of immune cell subsets and immunologic activity. The most speculative of these mechanisms at present is perturbation of the DNA damage response, but recent studies have shown that lenalidomide treatment of multiple myeloma is associated with phosphorylation of p53, and expansion of p53-mutant clones may occur during treatment of lower-risk MDS. Modified from Kotla et al. Professional illustration by Paulette Dennis.
arm of chromosome 5 (del(5q)) encouraged exploration of lenalidomide’s activity in other myeloid neoplasms, including higher-risk MDS and AML. After lenalidomide’s 2005 FDA approval for treatment of anemic patients with del(5q) lower-risk MDS, case reports of CRs in patients with AML associated with del(5q), trisomy 13, or other karyotypes prompted formal studies of lenalidomide in this patient population.

The activity of lenalidomide in some patients with excess marrow blasts was confirmed by a phase 2 clinical trial conducted by the Nordic MDS Group, and another by the Groupe Francophone des Myéloidyplasies (GFM) that enrolled patients with higher-risk MDS and del(5q). In the GFM trial, lenalidomide was administered at a starting dose of 10 mg for 21 of every 28 days, and was increased to 15 mg if there was no response. Hematologic improvement was noted in 27% of 47 enrolled patients, and 15% experienced cytogenetic responses. CRs were only observed in patients with a pretreatment platelet count > 100 × 10^9/L, all but 1 of the cytogenetic responders had isolated del(5q) rather than a more complex karyotype, and febrile neutropenia (sometimes lethal) was the most common adverse event. Similar response patterns were observed in the as-yet-unpublished Nordic study that also included some patients with del(5q) AML, in which the lenalidomide dose was escalated from 10 mg to 30 mg daily.

Investigators at The Ohio State University (OSU) enrolled 31 patients with relapsed or refractory AML with a variety of karyotypes in a phase 1 study; patients were treated with escalating doses of lenalidomide, from 25 to 75 mg daily, for 21 days in 28-day cycles. The maximally tolerated lenalidomide dose was 50 mg daily, and infectious complications were again common. Hematologic CR was achieved in 5 of 31 patients (16%), and these remissions lasted from 5.6 to 14 months; 3 patients—none with del(5q)—achieved cytogenetic CR. All of the patients who experienced CR in the OSU study had a low presenting leucocyte count, suggesting that lenalidomide’s activity is limited in patients with highly proliferative disease, even when high doses are employed.

Patients with relapsed/refractory AML are notoriously difficult to treat successfully, and some investigators believed that better results might be achieved with lenalidomide in the up-front setting. In a phase 2 trial conducted at Washington University in St Louis, 33 patients with untreated AML without del(5q) who were 60 years of age or older received lenalidomide 50 mg daily for up to two 28-day cycles, followed by maintenance at 10 mg daily. The CR rate, with or without platelet recovery, was 30%, with a median remission duration of 10 months. Similar to the OSU study, the CR rate was higher (50%) in patients with low circulating blast count (< 1.0 × 10^9/L) at diagnosis.

In this issue of Blood, Sekeres and colleagues report results from 37 evaluable patients aged 60 or older with newly diagnosed del(5q) AML enrolled in the S0605 cooperative group phase 2 study. Patients were treated with 50 mg/day of lenalidomide for 28 days, followed by a maintenance schedule of 10 mg/day for 21 of every 28 days. Approximately one-half (51%) of patients had antecedent MDS. The S0605 results are somewhat discouraging: only 38% of patients were able to complete the 28-day induction, and the median survival for the enrolled population was merely 2 months. Just 5 of 37 patients (14%) achieved either a partial response or CR, including 2 patients with isolated del(5q) and 3 with complex cytogenetics. These responses were not durable, with a median disease-free survival among responders of 5 months. The investigators appropriately conclude that lenalidomide has only modest activity in older patients with del(5q) AML.

Because of the relatively high cost of lenalidomide, potential adverse effects, low response rates, and lack of durability of most responses, the S0605 results should discourage off-label use of this agent in del(5q) AML. Responses that are seen, however, raise interesting questions about the mechanism of lenalidomide’s activity. Lenalidomide has pleiotropic biologic effects (see figure), which of these properties are responsible for the drug’s effectiveness in MDS, AML, or other conditions where lenalidomide is highly active (eg, multiple myeloma) remains enigmatic. The mechanism may be distinct in each disease state, as well as with higher versus lower drug doses.

That the highly encouraging results with lenalidomide in del(5q) lower-risk MDS were not repeated in del(5q) AML may not be surprising. These 2 disease states are similar with respect to blast presence, clinical behavior, prognosis, and molecular pathology. While haploinsufficiency of the RPS14 gene appears to be a key contributor to erythroid failure associated with del(5q) MDS, the critical genes responsible for clonal dominance in del(5q) AML are less well-defined and likely distinct, especially since the chromosome 5 commonly deleted region is different in these 2 settings. The S0605 study did not yield a new well-tolerated therapy useful for the majority of older adults with del(5q) AML. However, the clear activity of lenalidomide in a subset of patients with AML should promote ongoing efforts to identify those biologic features accounting for response, thereby allowing rational use of this agent, both alone and in combination approaches, for this highly challenging patient population.

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