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Comment on Whitlock et al, page 4043

## ALL in children with Down syndrome

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In this issue of *Blood*, Whitlock and colleagues from the Children's Cancer Group (CCG) present the largest series to date confirming prior observations that children with Down syndrome (DS) and standard-risk acute lymphoblastic leukemia (ALL) have an inferior outcome when compared with children with standard-risk ALL but without Down syndrome.

**D**own syndrome (DS) is the most common factor predisposing children to the development of leukemia. Three distinct patterns of leukemia have been well described in children with DS: transient myeloproliferative disorder (TMD), acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL). However, only recently have children with DS and leukemia been systematically enrolled on prospective clinical trials. In fact, for many years there was hesitation on the part of parents and physicians to aggressively treat many children with DS and leukemia.<sup>1,2</sup> The recent enrollment of these children on large cooperative group clinical trials has subsequently revealed numerous unique features about the epidemiology and biology of leukemia in these children, furthering our understanding of the mechanisms underlying leukemogenesis.<sup>1</sup>

Treatment strategies for children with DS and leukemia are now becoming apparent. It is now understood that most children with TMD will respond to close observation and supportive care, and most research efforts are now directed toward the early identification of children with high-risk TMD that would benefit from therapy. For AML, Gamiš et al<sup>3</sup> from the CCG recently demonstrated excellent outcomes for children with DS using therapy that was less intensive than that currently used for the treatment of AML in children without DS.

Whitlock and colleagues now present clinical and laboratory characteristics and outcomes for 179 children with DS and ALL who were treated on CCG protocols between 1983 and 1995, comparing these children to 8268 children without DS, also enrolled on the same prospective clinical trials. This retrospective analysis clearly demonstrates the inferior outcome of children with DS and standard-risk ALL when compared with children with standard-risk ALL but without DS. The reasons for a worse outcome in these DS pa-

tients is not clear, although possible explanations include a decreased prevalence of hyperdiploidy in DS patients, a favorable prognostic factor in childhood ALL.

Of interest, children with DS and high-risk ALL had outcomes comparable with children without DS but with high-risk ALL, perhaps suggesting the ability of DS patients to tolerate more aggressive treatment regimens, despite a known propensity for increased toxicities due to the altered metabolism of chemotherapy agents used to treat ALL (eg, methotrexate). Given the inferior outcome in DS children with standard-risk ALL, clinicians should use

caution when considering dose reductions for chemotherapy agents due to toxicity concerns in these children. Less intensive treatment could have an adverse effect on the outcome of these children.

As Lange so eloquently stated, "The current management strategy for these disorders, with few exceptions and considerable caution, is simple: in TMD, 'do nothing'; in AML, 'do less'; and in ALL, 'do more.'"<sup>1p512</sup> This study argues for "doing more" for standard-risk children with DS, with treatment on more intensive regimens or with therapy that is tailored to the unique biology of the DS host and leukemic blasts. ■

### REFERENCES

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Rajkumar et al, page 4050

## Myeloma therapy: the future is bright

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In a phase 2 study of lenalidomide combined with dexamethasone as front-line therapy for multiple myeloma, Rajkumar and colleagues report an excellent rate of responses, including 38% complete remission or near complete remission.

**O**ver the past decade, new insights into the biology of multiple myeloma have provided the framework for the development of novel therapies to reverse drug resistance and improve patient prognosis. In particular, recognition of the pivotal role of the bone marrow microenvironment in promoting myeloma cell growth, survival, drug resistance, and migration has allowed for identification of specific therapeutic strategies targeting myeloma-host stromal cells interactions, as well as the secretion of cytokines and their sequelae in the bone marrow milieu.<sup>1</sup> Examples of novel drugs that have quickly translated from the bench to the bedside include the first-in-class proteasome inhibitor bortezomib and immunomodulatory

analogs of thalidomide, known as immunomodulatory drugs (IMiDs).

Thalidomide, an old drug with a tragic past due to its teratogenicity, has redeemed itself as the third non-cross-resistant active antimyeloma agent and actually represents a new treatment paradigm for patients refractory to multiple prior therapies and with newly diagnosed disease.<sup>2</sup> However, marked activity of thalidomide is limited by dose- and duration-related side effects, which include peripheral sensory neuropathy, sedation, constipation, and skin rashes. In addition, when used as front-line therapy in combination with dexamethasone or anthracyclines, thalidomide is associated with an increased risk of deep vein