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## **Myeloma therapy: the future is bright**

Michele Cavo

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Whitlock et al, page 4043

## ALL in children with Down syndrome

Franklin O. Smith CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

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, Gams 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. ■

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Rajkumar et al, page 4050

## Myeloma therapy: the future is bright

Michele Cavo UNIVERSITY OF BOLOGNA

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

thrombosis, which requires prophylactic or therapeutic anticoagulation.<sup>2,3</sup>

The toxicity profile of thalidomide has prompted the search for more effective analogs with reduced toxicity. Based on promising preclinical data showing that the nonteratogenic IMiD lenalidomide (also known as CC-5013 or revlimid) is more potent than thalidomide in stimulating T-cell proliferation and increasing the production of interleukin-2 and interferon- $\gamma$ , as well as at decreasing the secretion of tumor necrosis factor- $\alpha$ ; phase 1, 2, and 3 clinical trials of this agent were performed in patients with advanced refractory or relapsed myeloma.<sup>4,5</sup> Favorable results of these studies ultimately led to incorporation of lenalidomide into front-line treatment strategies for multiple myeloma.

In this issue of *Blood*, Rajkumar and colleagues report on 34 previously untreated myeloma patients who were primarily treated with oral lenalidomide 25 mg/day for 21 days/month and oral dexamethasone 40 mg/day on days 1 to 4, 9 to 12, and 17 to 20, every month. Using the criteria of the European Group for Blood and Marrow Transplant, the overall rate of responses (partial and complete remissions) was 91%, including 38% of patients who achieved at least a near complete remission. Grades 3 to 4 side effects observed in more than 10% of patients included fatigue (15%) and neutropenia (12%). Toxicities commonly related to thalidomide were mild and well manageable; a single patient (3%) developed pulmonary embolism. Notably, lenalidomide was not toxic to hematopoietic stem cells that were adequately collected in a subgroup of patients who underwent this procedure. Although these results are exciting, formal validation of the role of lenalidomide as primary therapy for multiple myeloma has yet to be established. Two large randomized studies currently under way in the United States will address this important issue, and their conclusions are eagerly awaited.

After more than 3 decades without new active agents to treat multiple myeloma, the future is bright. Over the past few years, 2 new classes of drugs with the ability to sensitize myeloma cells to chemotherapy and/or to overcome drug resistance have entered the clinical practice. Although the impact of these novel treatment strategies and their combination with old drugs on the ultimate outcome of myeloma patients is still undefined, targeted therapies have greatly expanded the armamen-

tarium in the management of this still incurable disease. The new millennium has been an encouraging time for patients with myeloma, but the best is still to come. ■

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## ● ● ● HEMATOPOIESIS

Comment on Patel et al, page 4076, and Richardson et al, page 4066

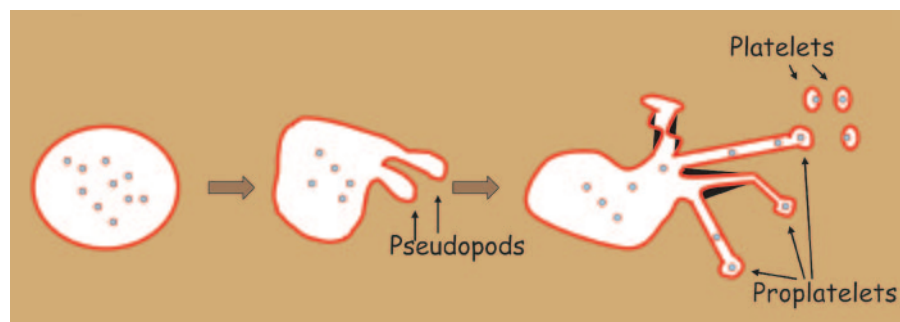
# Packing platelets to go

Charles S. Abrams UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE

In this issue of *Blood*, 2 companion articles by the Italiano lab give insight into the microtubule-mediated transport required for platelet production.

**W**e are approaching the 100th anniversary of James Homer Wright's seminal study of feline bone marrow that led him to postulate that platelets are fragments of megakaryocytes.<sup>1</sup> Despite this length of time, there is still controversy about the mechanism of platelet formation. There is some evidence to suggest that platelets are formed by fragmentation of the megakaryocyte cytoplasm. But several recent studies support the theory first proposed by Radley and Scurfield<sup>2</sup> that platelet production begins with an elaborate dance of the megakaryocyte requiring the extension of thick pseudopods (see figure). These pseudopods extend further and further, and be-

come quite thin, forming structures called proplatelets. Tablin et al<sup>3</sup> showed that proplatelets were filled with a cellular supportive network called microtubules. Microtubules serve as a highway to transport materials and information between the center and the periphery of the cell. Microtubules are composed of interlocking tubulin that are slowly generated and rapidly disassembled in most cells. Poisons of the microtubular system, such as vinca alkaloids, impair proplatelet and platelet production. Mice lacking a microtubule building block,  $\beta$ 1-tubulin, have reduced megakaryocyte proplatelets and produce only round platelets (but, curiously, still do make some platelets).<sup>4</sup>



**Platelets derive from megakaryocyte proplatelets. Microtubules aggregate at one end of the cell cortex of a megakaryocyte as the cell extends pseudopods. As pseudopods extend further, they become thinner and ultimately branch and split into proplatelets. Platelet granules and organelles are transported along microtubules through the proplatelets into the nascent platelets. Ultimately, platelets release off the ends of the proplatelets.**