with soluble IL-15Rα? Finally, are all naturally occurring soluble IL-15/IL-15Rα complexes equal? Can soluble IL-15Rα in humans act as an agonist in some situations and an antagonist in other situations? The current work by Bergamaschi and colleagues provides a strong foundation with which to address these and many other important questions relevant to the biology of IL-15 signaling. Furthermore, they provide a new paradigm for the consideration of cytokine function and signaling in vivo.

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**Comment on Cavo et al, page 9**

**Consolidation therapy in myeloma: a consolidated approach?**

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The use of a short consolidation treatment after autologous transplantation increases the complete response rate and relapse-free survival.

**Survival** in multiple myeloma has significantly increased in the past decade and this has been mainly due to the introduction of novel agents, such as immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib). However, how to optimally use these agents through the different phases of the disease has yet to be determined. In this issue of *Blood*, Cavo et al show that consolidation therapy with VTD (bortezomib, thalidomide, and dexamethasone) after double autologous stem cell transplantation (ASCT) is significantly associated with improved complete response rate (CR) and progression-free survival (PFS) compared with TD consolidation. This benefit was confirmed in the multivariate regression analysis, because VTD consolidation was identified as an independent variable favorably influencing PFS. Moreover, the toxicity was acceptable in consonance with the use of low-dose thalidomide (100 mg) and bortezomib (weekly schedule). In fact, only 1 patient with pre-existing neuropathy developed grade neuropathy.

A potential pitfall of this study is that patients who received VTD consolidation had already received VTD as induction whereas those allocated to TD consolidation were induced with TD. Therefore, it may be difficult to dissect the benefit of consolidation versus induction therapies. To overcome this potential bias Cavo et al performed a per-protocol analysis (excluding patients who discontinued treatment because of disease progression—more frequent in the TD arm—or because of adverse events). Using this approach, the CR rates after the second ASCT were not significantly different in the VTD and TD arms ($P = .13$); in contrast, after consolidation the CR rate was significantly higher with VTD compared with TD ($P = .012$).

In younger myeloma patients, the treatment goal for cooperative groups and large institutions should be to investigate curative treatment approaches. This implies integrating the best therapy for induction, consolidation, and maintenance. The evolving total therapy programs pioneered by the Arkansas group represent an example of this philosophy. Consolidation therapy here means a short-term treatment given to upgrade the quality of the responses obtained in the previous treatment phases. This goal was achieved in the present trial, particularly in the VTD arm, with 54.8% of patients achieving an upgraded response with consolidation. Unfortunately, the study design did not include minimal residual disease techniques (multiparametric flow cytometry or RQ-PCR) to evaluate the potential benefit of tumor reduction in patients who were already in CR before consolidation. It should be noted that this same group has previously reported that achievement of molecular responses after intensification with VTD is associated with long-term, relapse-free survival. Therefore, although there are long-term survivors who do not achieve CR but revert to a monoclonal gammapathy of undetermined significance-like status, for the majority of patients achieving and maintaining the best response would be a prerequisite for cure.

One of the most important findings of the Cavo et al study is the efficacy of VTD consolidation in patients with high-risk cytogenetics. Thus, in the cohort of patients with t(4;14) and/or del17p or just t(4;14), those who received VTD consolidation had a 63% relative reduction in the risk of progression compared with TD-treated patients. Moreover, the PFS curve of high-risk group was almost parallel to that of the standard-risk group, which indicates that VTD not only improves but overcomes the adverse prognosis associated with these cytogenetic abnormalities. It should be noted that this effect should not only be attributed to the consolidation therapy but to the integrated treatment, based on an optimized induction plus double autologous transplantation and consolidation. These positive results deserve 2 additional comments. (1) Although bortezomib appears to be an important drug for treatment of high-risk
patients, not all bortezomib-based studies have obtained the same positive results; therefore, attention should be paid to the subtle differences among trials. (2) Optimized treatments should not only be offered to high-risk but also, and particularly, to standard-risk patients because they are the first likely candidates for cure.

A final comment about overall survival: the study by Cavo et al does not show differences in OS between VTD and TD consolidation. This may be due to a short follow-up, or to differences in the rescue therapies used (which were not under trial control), or to the emergence of more resistant clones. This latter possibility is unlikely to be the explanation because the treatment duration of consolidation therapy is very short; therefore, the other options are more plausible.

Overall, this article highlights the benefit of VTD consolidation after double ASCT with emphasis in the high-risk population and although additional ongoing trials need to confirm these results, it is possible that “consolidation treatment” will become a “consolidated” part of the therapeutic scheme of younger patients.

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REFERENCES

Can computer models be designed to mimic in silico the calculations being performed by platelets as they respond to biochemical and biomechanical stimuli? Can these models be personalized to capture the phenotype of individual donors?

Platelet responsiveness to agonists can be highly variable among healthy human beings. Thus, a variety of candidate gene and genome-wide association studies are under way to identify the source of platelet hyperactivity. Further, platelets from certain patients exhibit diminished reactivity to drug or therapy. These features regulate patient clotting time and bleeding propensity. In this context, the work by Flamm et al suggests that understanding platelet phenotype regulation at the “systems-level,” by combining high-throughput experiments and related computations, can enable the evaluation of patient-specific cardiovascular risk and drug response (see figure).

Here, Flamm and colleagues perform high-throughput experiments to monitor platelet response to agonists against the platelet purinergic (ADP), thromboxane (U46619), and GPVI receptors (convulxin). Time-dependent changes in intra-cellular calcium are measured under a variety of conditions, and this is used to quantify platelet response to agonist. By varying the agonists over a wide range (0-10 times EC50) in pairs using a pairwise agonist scanning (PAS) scheme, calcium mobilization is measured in response to 74 different treatments for each donor sample. The large amounts of data generated in this manner are used to construct a donor-specific computer model of the platelet response (i.e., a “neural network” model). While this type of modeling is empirical in that it does not provide mechanistic or biochemical insights, it does represent a relatively simple yet powerful approach to capture the input-output response of platelets to both single and multiple complex agonists. Importantly, a separate platelet response model is generated for each blood donor, and thus subsequent experimental and modeling steps capture individual platelet phenotype.

To relate the measured platelet activation response to thrombus formation potential, multiscale computer simulations are performed. Here, mathematical equations of fluid transport, platelet motion, and cell adhesion are included in order to simulate thrombus growth rate under a variety of conditions.

Comment on Flamm et al, page 190

The computing platelet: integrating environmental cues

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In this issue of Blood, Flamm et al combine high-throughput experimental methods and multiscale computer simulations to predict patient-specific thrombus formation potential. Their studies reveal a novel thromboxane receptor mutation (TP-V241G) in humans that confers resistance to indomethacin.

Blood platelets integrate both biochemical stimuli and biomechanical cues to regulate their adhesive phenotype. At sites of injury, initial platelet attachment is mediated by von Willebrand factor (VWF), which forms a molecular bridge between platelets and extracellular matrix proteins. Subsequent thrombus formation rate is regulated by platelet response to multiple stimuli including collagen, ADP, thromboxane (TXA2), thrombin, epinephrine, and endothelial cell–secreted inhibitors like nitric oxide and prostacyclin. Fluid flow plays an important role in this process in part by regulating the binding interaction between platelets and VWF, initiating mechanotransduction, and controlling cell and solute transport in the vicinity of the thrombi. Platelet–platelet cohesion is strengthened by activated platelet integrin GPⅡb-Ⅲa, fibrin network formation, and signaling through integrins and receptor tyrosine kinases. Thus, despite the absence of a nucleus, these seemingly simple cell fragments have developed complex and calculating signal transduction pathways to integrate a variety of environmental cues and signals. The question then arises: Can computer models be designed to mimic in silico the calculations being performed by platelets as they respond to biochemical and biomechanical stimuli? Can these models be personalized to capture the phenotype of individual donors?
Consolidation therapy in myeloma: a consolidated approach?

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