Comment on Bergamaschi et al, page e1

Soluble IL-15/IL-15Rα complexes in human serum

David J. Cole and Mark P. Rubinstein MEDICAL UNIVERSITY OF SOUTH CAROLINA

In this issue of Blood, Bergamaschi and colleagues demonstrate that effectively all circulating IL-15 found in the serum of humans and mice is associated with the soluble IL-15Rα.1

Subsequent to the cloning of IL-15 in 1994, our understanding of how IL-15 signals and promotes lymphocyte function has been evolving, often in unexpected ways.2-5 Both IL-15 and its T-cell growth factor cousin, IL-2, mediate signaling through the shared IL-2/IL-15Rβγ. Initially it was thought that IL-15 would use the private IL-15Rα for high-affinity binding in a manner similar to IL-2, which uses the homologous IL-2Rα for high-affinity binding. However, the phenotype of IL-15−/− and IL-15−/−Rα−/− mice is virtually identical, and this suggested that IL-15Rα was functioning as more than merely a high-affinity receptor subunit. In fact, subsequent experiments showed, surprisingly, that IL-15 signaling was dependent on expression of IL-15Rα by nonlymphocytes.6 Thus, CD8 memory T cells failed to survive in IL-15Rα−/− hosts. Later experiments using bone marrow chimeric mice confirmed that functional IL-15 signaling depended on IL-15 and IL-15Rα expression in the same cell,7,8 suggesting that IL-15Rα is not simply a high-affinity receptor subunit but that it may aid in the transport of IL-15 outside the cell. This hypothesis was validated by 2 groups.9,10 Bergamaschi and colleagues elegantly demonstrated that the biologic activity of exogenous IL-15 depended on transfection of cells with both the IL-15 and IL-15Rα genes.9 They showed that not only do IL-15 and IL-15Rα interact at an intracellular level, but that the presence of IL-15Rα actually protected IL-15 from degradation. In addition, expression of IL-15Rα allowed for the accumulation of IL-15 on the cell membrane as well as in serum of mice. Mortier and colleagues reported similar results showing that IL-15Rα chaperones IL-15 to the cell surface in dendritic cells.10 They also were the first to demonstrate detection of soluble IL-15/IL-15Rα complexes in the serum of mice treated with TLR ligands. While multiple groups have been able to detect soluble IL-15Rα or IL-15 individually in serum samples, relatively little is known about the extent that these molecules are naturally associated (see figure). Making a significant methodologic advancement, Bergamaschi et al report the development of an ELISA assay able to recognize naturally occurring human IL-15/IL-15Rα complexes.1 Importantly, they excluded antibodies whose antigenic binding site were lost on association of IL-15 and IL-15Rα, and also tested their ELISA with IL-15/IL-15Rα complex standards produced in human cells with authentic glycosylation. Because it is difficult to detect IL-15 in healthy individuals, the authors used serum samples from melanoma patients who had undergone cytoreductive therapy. These patients are known to have detectable IL-15 in their serum. With this new assay Bergamaschi et al were able to successfully detect significant levels of IL-15/IL-15Rα in vivo.1 More importantly, however, they found that virtually all detectable IL-15 was associated with IL-15Rα. They also confirmed these findings in mice. In their murine model, they were able to detect IL-15/IL-15Rα complexes in normal serum as well as elevated levels of IL-15/IL-15Rα after treatment with either cyclophosphamide or total body irradiation. Importantly, they found that virtually all IL-15 in mice was associated with IL-15Rα similar to their findings in human serum.

While the work by Bergamaschi and colleagues provides important insight into the mechanisms of how IL-15 normally acts on lymphocytes, there still remain many important questions. For example, are membrane-bound IL-15 and soluble IL-15/IL-15Rα complexes both physiologically relevant, and to what extent? What are the biologic consequences of signaling when IL-15 is associated

---


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.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES


Comment on Cavo et al, page 9

Consolidation therapy in myeloma: a consolidated approach?

Jesús F. San-Miguel | HOSPITAL UNIVERSITARIO DE SALAMANCA

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).1 2 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.1 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 while those allocated to TD consolidation were induced with TD. Therefore, it may be difficult to disentangle 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.4 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.5 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.5 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.7 Therefore, although there are long-term survivors who do not achieve CR but revert to a monoclonal gammopathy 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.5 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
Soluble IL-15/IL-15Rα complexes in human serum

David J. Cole and Mark P. Rubinstein

Updated information and services can be found at:
http://www.bloodjournal.org/content/120/1/1.full.html

Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml