Peripheral Blood Stem Cells Reach New Heights

By Connie J. Eaves

Most drugs that have proven to be effective anticancer treatment agents are also highly toxic to cells of the blood-forming system. Thus, their optimal use is often a juggling act in which an attempt must be made to balance the benefit of intensifying the dose for an improved antitumor effect and risking an unacceptable (potentially lethal) period of myelosuppression. Ideally, the optimal regimen would be decided from quantitative information about the numbers and types of relevant tumor cells in any given patient as well as a knowledge of the minimum number and types of hematopoietic cells necessary to ensure a rapid and sustained blood count recovery. Unfortunately, such a goal is still hypothetical (possibly even unrealistically naive), although seminal advances in both tumor and hematopoietic stem cell biology continue to be made bringing the potential application of this type of approach closer and closer to clinical reality.

One of the first steps in this direction was the recognition that the myelosuppressive effects of intensified chemotherapy could be circumvented by the intravenous transplantation of a small fraction (<1%) of the total marrow of a normal individual, thus introducing the possibility of escalating the dose to levels that would otherwise be lethal. Not surprisingly, the utility of this strategy was first explored clinically in patients with hematologic malignancies of poor prognosis where the tumor population frequently shows the same type of radiation and drug sensitivity characteristic of the normal cells in which the transformation events occurred. The subsequent successful development and expansion of this principle, as recognized by the award of a Nobel prize in 1990 to its prime engineer, Dr E. Donnall Thomas, has now stimulated considerable further interest in its potentially useful extension to other, more common, chemosensitive tumors of nonhematopoietic origin, including germ cell tumors and breast cancer. Because of the still severe side effects associated with the transplantation of allogeneic bone marrow (BM), interest has grown in the use of the patient's own (autologous) cells for hematologic rescue and in the additional possibility of exploiting such cells as vehicles for various gene therapy strategies. Thus, there is a rapidly growing clinical demand for hematopoietic transplants and a strong rationale for studies that will make this procedure cheaper and easier to pursue on a larger scale.

Over the last 5 to 10 years this pressure has translated scientifically into a dramatic increase in our understanding of the extensive hierarchy of primitive hematopoietic cell types that is established during ontogeny, as well as a more sophisticated appreciation of the complexity of parameters that may influence the recruitment and longevity in vivo of those that have repopulating potential. Concurrent with this expansion in knowledge of stem cell biology has been the identification and cloning of a large array of growth factors whose activities, both in vivo and in vitro, can have marked effects on the growth and functioning of various hematopoietic cell precursors. One such effect, not predicted by in vitro experiments, is the ability of many of these growth factors to promote an exodus of primitive hematopoietic progenitors from the BM into the peripheral blood. This latter discovery has focussed considerable recent attention on the potential use of peripheral blood harvests as an adjunct to, or even as a substitute for, marrow cell transplants in patients given myeloablation therapy.

Studies in mice attest to the ability of such peripheral blood cell preparations to provide not only immediate, but also the sustained output of all types of blood cells in lethally irradiated recipients. These findings help to counteract a historical concern that, in humans, blood cell transplants may have a relatively low content of long-term repopulating cells with extensive self-renewal capacity and may, therefore, be unable to sustain blood cell production after a few weeks despite their obvious ability to give early count recovery. However, extrapolation from mouse to human must also be regarded with caution. On the other hand, the lack of a sensitive and rigorous in vivo system for identifying and quantitating the types and numbers of primitive human hematopoietic cells that need to be infused after myeloablative therapy currently precludes validation of results obtained in mice. Hopefully, improvements in xenogeneic transplant models may change this situation in the future. In addition to these questions, there is the possibility that the process of progenitor mobilization, or events associated with progenitor mobilization, may initiate qualitative changes in hematopoietic progenitors that affect their potential for homing, amplification, and/or differentiation on transplantation.

Clearly one approach to investigating these various issues is to use currently available in vitro procedures to measure and compare the mobilization kinetics of different classes of progenitor cells observed after different types or numbers of mobilization treatments, and then to correlate the numbers of progenitors collected and autografted with various hematologic recovery parameters. Measurements of a number of distinct subpopulations of progenitor cells are now possible. Many are routinely detected by virtue of their ability to proliferate and differentiate in response to various known growth factors or similarly stimulatory conditioned media in semisolid culture media. These colony-forming cells (CFC) can be subdivided into different classes according to the different numbers and types of differentiated progeny they produce under conditions of maximal stimulation.
In addition to the various lineage-restricted and pluripotent CFC identified by these relatively short-term assays, it is now possible to detect and quantitate other, more primitive cells that give rise to CFC for many weeks when stimulated by unknown factors produced by marrow adherent cells and certain fibroblast cell lines. These progenitors are referred to as long-term culture-initiating cells (LTC-IC) and are of particular interest in that most show phenotypic properties that are characteristic of long-term repopulating cells in the mouse and that, at the same time, allow them to be separated from most CFC. Recent studies indicate that LTC-IC (like CFC) may represent a biologically heterogeneous population including members of differing phenotype and proliferative potential, the latter property being reflected by the duration of their ability to produce daughter CFC and (unpublished findings, 1993).

There is also a growing interest in the possibility that different types of progenitors can be measured directly by multiparameter phenotyping of CD34+ cells or subpopulations. This approach has the significant advantage that the results are essentially immediate and can therefore, at least in theory, be used to guide clinical decisions based on the measured composition of a particular transplant. However, although this approach may be empirically useful for some applications, phenotypic correlates of progenitor function are still not refined enough to allow reproducible and meaningful discrimination between different types of functionally defined progenitors.

The report in this issue by Pettengell et al represents an excellent example of how monitoring the progenitor content of the peripheral blood in patients treated with multiple courses of chemotherapy and granulocyte colony-stimulating factor (G-CSF) may provide important clues to the improved use of peripheral blood autografts. First, these studies show the remarkable levels that mobilized CFC and LTC-IC can achieve in the peripheral blood such that they may equal or even exceed the concentrations of these cells in steady-state normal marrow. From a practical point of view, this means that it may be relatively easy to obtain an adequate number of progenitors for various transplant applications from a single leukapheresis collection. The findings reported in this study are also significant in their documentation of the utility of the rising white blood cell (WBC) count, at least in certain disease settings (as was the case here for high-grade non-Hodgkin’s lymphoma) to predict the time for collecting maximally, or near maximally mobilized when the WBC count reached 5 to 10 x 109/L after each of six or more cycles of the treatment had been completed.

Given the evidence that the transplantation of mobilized peripheral blood progenitors can significantly reduce the period of neutropenia and thrombocytopenia that follows the transplantation of marrow autografts into myeloablated patients, the question still paramount to the field as a whole is whether the cells infused also contribute to the sustained hematopoiesis that ensues, an issue that will only be definitively resolved by gene marking studies. Also important is the practical question of how well the results shown in the Pettengell study will provide pointers for other patient categories or treatment regimes, particularly those where previous experience suggests greater variability in progenitor mobilization, either because of previous chemotherapy or extensive disease involvement of the marrow. Nevertheless, even with these questions unanswered for some time to come, it would appear that mobilization of early hematopoietic cells into the peripheral blood already offers unanticipated opportunities to facilitate the use and eventual evaluation of more intensive treatment regimes for patients with cancer.

REFERENCES

progenitor cells mobilised by filgrastim (G-CSF) on platelet recovery after high-dose chemotherapy. Lancet 339:640, 1992
Peripheral blood stem cells reach new heights [editorial; comment]

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