that target vascular inflammation, such as the statins, may effectively control the enhanced coagulant activity that is so prominent in patients with SCD.

REFERENCES

Comment on Pfreundschuh et al, page 626, and on Pfreundschuh et al, page 634

Is more better?

David Linch University College London

Two parallel trials reported in this issue of Blood suggest that intensified CHOP is superior to standard CHOP in the management of histologically aggressive NHL. These studies also suggest that different strategies for dose intensification may be optimal in different patient subgroups.

Ever since the introduction of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) combination chemotherapy for the treatment of histologically aggressive non-Hodgkin lymphoma (NHL), attempts have been made to further improve the results by intensifying the therapy administered. Previous escalated regimens have been largely disappointing when tested in large randomized trials, as exemplified by the National High-Priority Lymphoma Study, in which m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone), MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin), and Pro-MACE-Cytar-BOM (cyclophosphamide, doxorubicin, etoposide, prednisone, cytarabine, bleomycin, vincristine, methotrexate) were shown to be no better than CHOP. This might indicate that intensification of CHOP is of no value, but alternatively it may be that the so-called escalated regimens were not significantly more intensive than the original CHOP regimen. As more drugs were added to the CHOP regimen and/or dosing intervals were reduced, it became necessary to reduce the dose of some agents and it is possible that these reductions were made in the most efficacious drugs. The calculations of relative dose intensity (RDI; according to the method of Hryniuk and colleagues) are confounded by the lack of large or randomized single-agent trials, so the assignment of the relative efficacies of individual components of a regimen is, at best, approximate.

Hasenclever and colleagues, building on the Skipper et al model, have proposed the concept of the effective dose approach, which takes into account not only the total dose of chemotherapy and RDI but also the heterogeneity of histologically aggressive NHL with respect to chemosensitivity and tumor growth rate. They hypothesize that in rapidly growing lymphomas (identified at presentation by the surrogate marker of a raised lactic dehydrogenase [LDH] level), tumor regrowth between cycles is a potential problem and the way forward is to increase the dose intensity by shortening the interval between cycles whilst maintaining the same dose per cycle. This is now achievable with the use of granulocyte colony-stimulating factor (G-CSF). In patients with a low LDH level, by contrast, the optimal approach may be to keep the intervals the same and increase dose intensity either by increasing the dose of one or more agents or by adding in an additional efficacious agent without reducing the doses of the original drugs.

In this issue of Blood, Pfreundschuh and colleagues report on the prospective testing of this model in 2 large trials with the same 2 × 2 factorial design investigating whether shortening the intervals and/or adding etoposide could improve event-free survival (EFS).

In the NHL-B2 trial for patients older than 60 years (40% of whom had a raised LDH level), an interaction between the 2 randomizations prevented the intended analysis. However, considering the 4 arms separately, the EFS and overall survival (OS) were significantly longer with the dose intensification achieved with CHOP-14 (CHOP given every 2 weeks) compared with the other 3 regimens. Rather surprisingly, CHOP-14 given with G-CSF was not much more toxic than CHOP-21 (CHOP given every 3 weeks), but it should be noted that only 14% of patients had an age-adjusted International Prognostic Index (IPI) score of 2, and 5.2% had a score of 3, which is considerably lower than in most other
series and trials of patients of 60 years or older. Some caution must still be exercised, therefore, in the extrapolation of the safety results to a less-selected elderly population.

In the NHL-B1 trial, for good-risk (normal LDH level) adult patients of 60 years of age or younger, the addition of etoposide, but not interval reduction, led to a significant improvement in EFS. The results of the standard CHOP-21 arm in this trial appear rather poor (EFS at 5 years of 54.7%), bearing in mind that all patients had low or low-intermediate IPI risk, but nearly 28% did have bulky disease, which might influence the results.

These results and those of the NHL-B2 trial provide support for the effective dose model, although it is disconcerting that in the NHL-B1 trial, the improvement in EFS with etoposide did not lead to an improvement in OS; in fact there was a significant improvement in OS with interval reduction, as in the trial for older patients.

The authors of these papers conclude that they have defined new “preferred therapies” for histologically aggressive NHL, but the standard therapy today (although not when these trials were started) is not CHOP-21, it is CHOP-21 plus rituximab. Although rituximab may add further to the benefits of CHOP-14 or CHOEP-21 (CHOP plus etoposide), it is possible that the use of rituximab may negate any benefits due to dose intensification. In the rituximab era, it remains unclear whether “more is better,” and further trials are required.

REFERENCES

Comment on Wagner et al, page 675

**Stem cells and the Heisenberg uncertainty principle**

**H. Jeffrey Lawrence  UNIVERSITY OF CALIFORNIA–SAN FRANCISCO**

Considerable efforts have been directed at understanding the distinctive genetic programs that underlie the biology of the elusive hematopoietic stem cell.

In this issue of Blood, Wagner and colleagues publish another gene expression profile of human hematopoietic stem cells (HSCs), using the novel strategy of isolating the slow-dividing fraction (SDF) of CD34+CD38- cells. This SDF is determined by its failure to divide after a week in culture, as measured by the retention of the membrane dye PKH26. The rationale for this study is that functional HSCs are largely quiescent, a view supported by a sizeable body of prior evidence.1 Although this study is technically rigorous, an obvious concern is that the isolation procedures and the time in culture alter the transcriptome of these cells, even though they have not divided. As Theise2 has recently pointed out, all the various manipulations used by different investigators to isolate HSCs (fluorescence-activated cell sorting [FACS], magnetic beads, dye exclusion, and dye retention) may perturb the biology of stem cells that have been ripped from their native environment, thereby, to paraphrase Heisenberg, disturbing the very phenomenon under study.

Another concern with this and all other published HSC gene expression profiles is comparability between studies. Considering that the isolation strategies vary considerably from study to study, as do the original sources of cells, the analytic platforms used, and even the statistical methods applied, it is probably not surprising that the degree of overlap between surveys is limited (Wagner and colleagues [Table 6]). These results suggest that different investigators may in fact be looking at distinct cells or mixtures of cells and introduce uncertainty as to what the transcriptome of the “real” HSC is. Indeed, the comparability of the profiles of CD34+CD38- cells and SDF cells within this study is low, with only one gene, osteopontin, showing high levels of differential expression in both sets of cells (Wagner and colleagues [Tables 1 and 3]).

Putting these significant technical concerns aside, these authors are to be commended for using a functional attribute of stem cells, proliferative quiescence, as part of their enrichment strategy. A more distinctive functional attribute of stem cells is their capacity for asymmetric division, leaving one daughter stem cell and sending the other sibling down the differentiation pathway. These authors’ own previous work demonstrated that approximately 30% of CD34+CD38- cells appear to divide asymmetrically, giving rise to one quiescent and one proliferating daughter.
Is more better?

David Linch