as the International Staging System 3 or chromosomal abnormalities, such as t(4;14), t(14;16), and del(17). Suboptimal response in the early phases of treatment may represent an advantage over biological markers for the treatment choice of an individual patient.

A suboptimal response might influence physicians’ decisions on prolongation of induction therapy from 3 to 6 cycles. It might suggest an increasing of the potency of the induction regimen, moving from a 2-drug combination to a 3-drug combination that includes an additional agent, either novel agents or doxorubicin or cyclophosphamide.

The advantage of a tandem, instead of a single, transplantation in patients with suboptimal response after induction therapy or in those with less than complete response after the first transplantation should be considered. Few data are available on the role of consolidation and maintenance therapy after autologous stem cell transplantation. But similarly, the expectation of poor outcome predicted by suboptimal response after induction therapy might suggest the introduction of a consolidation approach after autologous transplantation, such as bortezomib-cyclophosphamide-dexamethasone, bortezomib-lenalidomide-dexamethasone, or bortezomib-thalidomide-dexamethasone combination. Maintenance therapy is an alternative strategy. Three different phase 3 studies found that thalidomide maintenance improved progression-free and overall survival. Lenalidomide may offer the same advantage with less toxicity and large randomized trials are now addressing its role in the posttransplantation setting. More recently, data on bortezomib maintenance are also showing efficacy in this setting.

Further studies are needed to assess the role of tailored therapies in patients with poor outcome. The study presented by Gertz et al clearly shows that patients who do not reach at least partial response after induction therapy will do considerably worse and different treatment approaches are needed. Whether intensification of induction, use of tandem transplantation, introduction of consolidation, or maintenance therapy are the appropriate choices to overcome poor outcome still remains an open question. Despite this, in newly diagnosed patients, it is reasonable to use all available options to improve suboptimal responses.

On the other hand, we should avoid the risk of undertreating patients with good tumor reduction after induction therapy or autologous transplantation. In a recent analysis, only patients who achieved at least very good partial response after autologous stem cell transplantation received a consolidation with the 3-drug combination, bortezomib-thalidomide-dexamethasone. In these good-prognosis patients, the addition of consolidation after transplantation improved the complete response rate from 15% after transplantation to 50% after consolidation. The absence of a consolidation approach in patients with very good partial response after transplantation may significantly decrease the possibility to achieve a complete response.

In good-prognosis patients, the best treatment option, validated by large phase 3 studies, should be always considered to maximize the chance of a profound tumor reduction and a prolonged remission duration. In patients with poor prognosis, a more intense approach should be offered. The lack of a partial response after induction therapy with novel agents should now be considered another sign of poor prognosis and should suggest an intensification of the reference treatment.

**CLINICAL TRIALS**

Comment on Pennell et al, page 2364

Iron chelation therapy: you gotta have heart

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The study by Pennell et al in this issue of Blood reports the effect of the orally active iron chelator deferasirox on cardiac iron and function in patients with thalassemia major.

For decades, clinicians have recognized that cardiac iron accumulation is the critical problem in patients receiving long-term transfusion therapy with red cells. Cardiac failure and arrhythmias are the leading causes of death in patients with thalassemia. In the absence of a safe and accurate method to assess cardiac iron content directly, measures of iron in the more accessible liver or conventional tests of cardiac function such as ejection fraction have been used to predict who might be at risk for deadly cardiac complications. The former is frequently misleading, and the latter is too little too late. The application of magnetic resonance techniques, particularly T2*, has at last provided a tool to quantify cardiac iron repeatedly and noninvasively. T2* values less than 20 ms reflect increased cardiac iron stores and values less than 6 ms are associated with...
a very high risk for imminent heart failure.1 Cardiac T2* studies have also dispelled the notion of a consistently close relationship between liver and cardiac iron,2 and have established direct measurement of cardiac iron as a (if not the) critical outcome in assessing the efficacy of iron chelation therapy.

As a result, we are now gaining increasing clarity about the effects on the heart of the 3 iron chelators that are available in different parts of the world. In randomized, controlled clinical trials in patients with thalassemia and mild to moderate cardiac iron overload, deferiprone, still unlicensed in North America but widely available elsewhere, has proven more effective than deferoxamine in improving cardiac T2* and ejection fraction,3 and the combination of deferiprone and deferoxamine has proven more effective than deferoxamine alone in improving cardiac T2* and ejection fraction.4 Combined therapy with deferoxamine and deferoxamine has been similarly effective in the particularly vulnerable patients with severe cardiac iron overload and low ejection fractions.5 These studies support important earlier observations about the effectiveness of deferiprone in preventing cardiac death in patients with thalassemia.6

The present multicenter, prospective study of the newest iron chelator, deferasirox, by Pennell et al evaluates changes in cardiac T2* and ejection fraction over 12 months in a large cohort of patients with thalassemia and ejection fractions of 56% or higher.7 In patients with cardiac iron overload (T2* 5-20 ms), the mean T2* improved from 11.2 ms to 12.9 ms; increases occurred in 70% of patients. In patients without significant cardiac iron overload (baseline T2* values > 20 ms), the mean T2* did not deteriorate, and no patient fell below 20 ms at the end of the study. In contrast to the earlier studies of deferiprone, the mean ejection fraction did not improve in patients with cardiac iron overload treated with deferasirox, although improvement occurred in patients with normal cardiac iron.

The dosing of deferasirox in this trial deserves particular attention. Novartis recommends a starting dose of 20 mg/kg/day. However, most patients with cardiac iron overload began the study at a deferasirox dose of 30 mg/kg/day. By the end of the study, 63% required 40 mg/kg/day, the highest currently approved dose, to reduce cardiac iron. Most patients without increased cardiac iron entered the study at a dose of 20 mg/kg/day, but almost one-half required 40 mg/kg/day of deferasirox to maintain a normal cardiac T2*. These dose requirements support the experience of clinicians that patients with thalassemia frequently need a higher dose of deferasirox and excellent compliance to remove excessive iron or to prevent further iron accumulation. Fortunately, the safety profile of deferasirox at a dose of 40 mg/kg/day resembles the profile at lower doses. However, the cost of the higher doses approaches $80,000 per year for an adult and dramatically widens the gap between the cost of deferasirox and other chelators.8 Compliance must be watched very carefully, as it is generally poorer outside of clinical trials.

What additional studies will help clinicians and patients navigate the historically stormy waters of iron chelation therapy? The authors point out that a study comparing deferasirox and deferoxamine is currently under way. Although deferoxamine as a daily subcutaneous infusion has proven to be a very effective chelator, the widespread adoption of orally active chelators suggests that the days of deferoxamine as monotherapy are largely over. With 2 orally active chelators now available and with tools for noninvasive measurement of cardiac iron now accessible, studies of new combinations of chelators and a direct comparison of the effectiveness of deferiprone and deferasirox in addressing cardiac iron and improving survival will likely guide the future management of transfusional iron overload.

Conflict-of-interest disclosure: A.R.C. serves on a DSMB for ApoPharma for which he receives reimbursement for meeting-related expenses.

REFERENCES

HEMATOPOIESIS & STEM CELLS

Comment on Staron et al, page 2380

Chaperoning the lympho-stromal dance

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In this issue of Blood, Staron and colleagues reveal an unexpected and nonredundant role for gp96 in the early development of B and T cells that may help to better define the critical role of integrins in lymphopoiesis.1 Initially identified as a glucose-regulated protein, gp96 (also referred to as grp94 or tumor rejection antigen 1) is an abundant endoplasmic reticulum protein with multiple biologic functions.2 As a chaperone molecule during protein folding, gp96 is up-regulated during cell stress and plays a key role in unfolded protein responses (UPR). When released into the extracellular milieu after necrosis, soluble gp96 can function as an adjuvant for antitumor immune responses and can activate macrophages through Toll-like receptor 2 (TLR2). In addition, gp96 can bind short peptides and

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