matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF, Bruker Ultraflex, Bremen, Germany) mass spectrometer. We found several proteins that were differentially expressed between pre-ASCT and control fibroblasts. Proteins involved in growth suppression (Figure 1Ai,v,viii) were down-regulated (MnSOD,6 28-fold decrease; Cu/Zn SOD1,7 absent) in pre-ASCT fibroblasts, whereas those implicated in increased proliferation were up-regulated (stathmin,8 absent; profilin I,9 absent; and macrophage inhibitory factor,10 reduced 8.65-fold). After ASCT (Figure 1Aiii,vi,ix), all proteins that were abnormally down-regulated or up-regulated reached normal levels (ie, those observed in control fibroblasts) (Figure 1Ai,iv,vii). Interestingly, we also observed a reversal of the pre-ASCT fibroblasts’ 2D protein expression profile with all the drugs tested (Figure 1B).

As our patient is clinically asymptomatic and relapse-free 3 years after treatment, we propose that the pre-ASCT conditioning regimen (BEAM), which includes a combination of hypo/hypermethylating drugs, may help to avoid the relapses observed in patients treated with melphalan alone. Our results show that (1) the conditioning regimen and ASCT used in our patient can produce a permanent remission in severe scleromyxedema; (2) fibroblasts proliferate aberrantly in vitro in patients with scleromyxedema, and this can be reversed with chemotherapeutic drugs such as BCNU, Ara-C, and melphalan; and (3) monoclonal gammopathy, at least in our patient, is not responsible for the fibroblast proliferation. In conclusion, a constitutive proliferation of fibroblasts, independent of serum factors, seems to be the key pathologic feature in scleromyxedema and can be steadily reversed with the BEAM regimen in severe cases.

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References


To the editor:

Deferasirox versus deferoxamine

Cappellini and colleagues1 recently published the results of the first large, randomized phase 3 trial comparing deferoxamine (DFO) and deferasirox, a trial designed to demonstrate the efficacy of deferasirox in regularly transfused patients with β-thalassemia. The efficacy of a drug is its ability to produce a specific effect in a specific patient population. Effectiveness is a measure of efficacy in the “real world,” outside the bounds of a randomized clinical trial; it explores compliance, generalizability, and external validity.2 DFO is efficacious, but its effectiveness is limited mainly by poor compliance. It is anticipated that deferasirox, as a once-daily oral medication, might exhibit improved effectiveness over DFO.

In the trial by Capellini and colleagues, when the primary end-point analysis failed to prove noninferiority despite adequate power, the data were reanalyzed using a nonprespecified subgroup analysis to show noninferiority in those patients with baseline liver iron concentrations of 7 mg Fe/g dry weight (dw) or higher dosed with 20 to 30 mg/kg deferasirox, thereby retrospectively excluding approximately 30% of the patients randomized to the deferasirox arm. The reported tolerability and safety data, on the other hand, take into account the entire patient population randomized to take deferasirox, not the nonprespecified subgroup, in which noninferiority to DFO was demonstrated. In order to provide a better
understanding of the potential effectiveness of deferasirox, it would be helpful to report the compliance, tolerability, and adverse event rate data stratified by dose.

Mike G. Martin and Murat O. Arcasoy

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Response:

Deferasirox (ICL670) is clinically effective and generally well tolerated, and demonstrates dose-responsiveness

As Martin and Arcasoy observed, noninferiority to deferoxamine (DFO) was demonstrated in patients with baseline liver iron concentrations (LICs) of 7 mg Fe/g dry weight or greater (71% of the deferasirox-treated population), who were assigned doses of 20 or 30 mg/kg per day. We agree it is useful to determine both the efficacy and effectiveness of deferasirox and to review tolerability and safety data by dose.

It is generally recognized that randomized, controlled clinical trials are inadequate to measure “real-world” compliance and that drug counts do not effectively measure compliance. We collected actual feedback from patients by measuring satisfaction with and convenience of treatment. Significantly more patients receiving deferasirox, all of whom had previous experience with DFO, were satisfied with treatment and found it to be more convenient than DFO. Patients also found that deferasirox had less effect on daily life, and many more patients were willing to continue deferasirox after the end of the study; similar results have been observed in patients with sickle cell disease. These results could provide important information for clinical practice. Superior satisfaction with and convenience of deferasirox therapy versus DFO may translate into actual patient compliance and may therefore increase the effectiveness of chelation therapy, optimizing the outcome of iron-overloaded, transfusion-dependent patients.

Deferasirox treatment was generally well tolerated in patients aged 2 years and older. Dose adjustments/interruptions (36.8% versus 33.1%, respectively) and discontinuations (5.7% versus 4.1%, respectively) were similar with deferasirox and DFO (Table 1). We note that adjustments in the groups given 5 or 10 mg/kg per day were primarily due to insufficient dosing rather than safety concerns (87.5% and 42.7%, respectively). The most common deferasirox-related adverse events (AEs) were mild to moderate transient gastrointestinal (GI) events. Skin rash and mild, nonprogressive dose-dependent serum creatinine increases were also observed in deferasirox-treated patients (Table 1). Regarding the creatinine increases, it is possible that the glomerular filtration rate is reset as observed with other drugs such as ACE (angiotensin converting enzyme) inhibitors. Preliminary analyses indicate that the volume of blood transfused is inversely related to nonprogressive creatinine increases; further analyses to fully evaluate this relationship are ongoing.

A clear dose response was observed with no reduction in efficiency, indicating that the dose of deferasirox can be tailored for each patient depending on her or his need (ie, maintenance or reduction of body iron levels). We note that the response to deferasirox is not only influenced by dose but also by the rate of transfusional iron intake. This factor must also be considered when defining the therapeutic dose for a patient.

In closing, deferasirox doses of at least 30 mg/kg per day are generally well tolerated in β-thalassemia patients as young as 2 years. The overall discontinuation rate with deferasirox was low, and most reported AEs were transient and managed by dose modification or comedication. It is thought that, in clinical practice, the low discontinuation rate will be reproduced, and that the greater satisfaction and convenience compared with DFO will translate into improved patient compliance. This should lead to increased effectiveness compared with current chelation therapy.

Maria Domenica Cappellini

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Table 1. Tolerability and safety parameters, stratified by dose

<table>
<thead>
<tr>
<th>Total no. of patients</th>
<th>Total</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose ± SD, mg/kg/d</td>
<td>19.9 ± 8.3</td>
<td>6.2 ± 1.6</td>
<td>10.2 ± 1.2</td>
<td>19.4 ± 1.7</td>
<td>28.2 ± 3.5</td>
</tr>
<tr>
<td>Dose adjustments, no. of patients (%)</td>
<td>109 (36.8)</td>
<td>8 (53.3)</td>
<td>24 (30.8)</td>
<td>28 (33.3)</td>
<td>49 (41.2)</td>
</tr>
<tr>
<td>Discontinuations, no. of patients (%)</td>
<td>17 (5.7)</td>
<td>0 (0)</td>
<td>8 (10.3)</td>
<td>3 (3.6)</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>GI events, no. of patients (%)</td>
<td>45 (15.2)</td>
<td>1 (6.7)</td>
<td>9 (11.5)</td>
<td>12 (14.3)</td>
<td>23 (19.3)</td>
</tr>
<tr>
<td>Skin rash, no. of patients (%)</td>
<td>32 (10.8)</td>
<td>0 (0)</td>
<td>8 (10.3)</td>
<td>7 (8.3)</td>
<td>17 (14.3)</td>
</tr>
<tr>
<td>Nonprogressive creatinine increases, no. of patients (%)</td>
<td>113 (38.3)</td>
<td>1 (6.7)</td>
<td>15 (19.2)</td>
<td>33 (39.3)</td>
<td>64 (53.8)</td>
</tr>
<tr>
<td>Increases above ULN, no. of patients (%)</td>
<td>7 (2.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (3.6)</td>
<td>4 (3.4)</td>
</tr>
</tbody>
</table>

ULN indicates upper limit of normal.
*Drug-related AEs only.
†All AEs, irrespective of relationship to study drug.

References


2. Rothwell PM. External validity of randomized clinical trials: to whom do the results of this trial apply? Lancet. 2005;65:82-93.
To the editor:

Misclassification of amyloidosis is unwarranted

The article by Comenzo et al1 addresses a seminal issue; namely, the therapeutic necessity of establishing the identity of the protein contained in amyloid deposits. They found, as did Lachmann et al,2 that certain patients presumed to have immunoglobulin light-chain (AL) amyloidosis based on clinical and laboratory criteria (including the presence of a monoclonal gammopathy) in fact did not, but rather had a different form that resulted from a mutation in a gene encoding amyloidogenic precursor proteins (eg, transthyretin [TTR]). Given that individuals diagnosed with AL amyloidosis could be subjected to high-dose melphalan and stem cell transplantation—an intensive and potentially lethal therapy—it is essential that the nature of the amyloid-forming protein be unequivocally established.

The aforementioned reports emphasize the fallacy of relying on indirect evidence to ascertain if an individual has AL amyloidosis or some other kind of amyloid disease. Notably, the presence of a monoclonal protein, an altered serum k/λ ratio, or a mutated gene may represent confounding factors that do not necessarily reveal the true composition of the congophilic deposit, thus making a precise diagnosis impossible. Further, although the type of amyloid present in pathologic deposits may avoid diagnostic errors, especially in the case of AL amyloidosis, where patients could be subjected to inappropriate and costly therapy that can have untoward and possibly legal consequences.

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Response:

Constraints on the pursuit of diagnostic confidence

We agree with the critique offered by Solomon and colleagues but hasten to add that there are a series of constraints on the effort to obtain a “true diagnosis” in patients with amyloidosis and 2 possible fibril-precursor proteins. The proximal constraints are specimen related, assay related, and clinical. The overarching constraint is that our knowledge of the fundamental processes of amyloid fibril formation and amyloid disease remains so limited.1,2

Specimen-related constraints involve the accessibility of biopsy material containing amyloid and the amount of amyloid such biopsies contain. Surrogate biopsies from abdominal, rectal, or gingival tissue are negative a significant fraction of the time, and involved organ biopsies in patients with isolated cardiac or peripheral nervous system amyloidosis frequently contain minimal amounts of amyloid. The possibility that oligomeric intermediates on the path to fibril formation may be toxic, particularly to the heart and nerves, is consistent with these findings.3 Admittedly, sophisticated techniques for amyloid protein extraction and identification have been described by Solomon and colleagues, but the constraint on these assay techniques is that they have not been validated in large numbers of samples in multiple

References

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