and RUNX1b/c is increased during the hematopoietic differentiation of human ES/IPS cells, and that RUNX1b/c expression is always higher than RUNX1a expression. This was illustrated in Ran et al, Figure 1A-B, and supplemental Figure 1.

Finally, Real et al questioned whether the engraftment we observed by CD45+ CD34+ HSPCs derived from RUNX1a-expressing human ES cells was due to an intrinsic feature of the HSPCs, or simply because we transplanted an unusually large number of HSPCs. At present, we cannot distinguish between those 2 possibilities. However, regardless of the mechanism, overexpression of RUNX1a permitted engraftment, either by promoting expansion of HSPCs in vitro, or by altering the properties of HSPCs in vivo; determining which is the case will be a focus of future studies.

In short, we demonstrate a positive effect of RUNX1a on promoting hematopoiesis from human pluripotent stem cells, which provides a potential novel avenue for generating therapeutic HSCs. Additional studies are necessary to examine its possible transforming ability and to create inducible expression systems for using RUNX1a in regenerative medicine.

To the editor:

Young adults with acute lymphoblastic leukemia treated with a pediatric-inspired regimen do not need a bone marrow transplant in first remission

Gupta et al concluded that young adult patients with acute lymphoblastic leukemia (ALL) aged 15 to 35 years should be treated in first remission with allogeneic transplant. They based their judgment on a meta-analysis of 13 studies, each of which had a control regimen

References


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used historically for adult patients, such as hyper-fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone, as the comparator. Although they did state that “... several groups have reported good outcomes of standard risk adult ALL patients treated with pediatric-inspired chemotherapy protocols,” we submit that this acknowledgment should be the crux of a different conclusion rather than a passing comment.

Table 1 lists outcomes from multiple adult and pediatric studies in North America and Europe that treated adolescent and young adult ALL patients. When comparing survival of patients treated using a regimen from an adult-based consortium with either a pediatric consortium or an adult consortium utilizing a pediatric-inspired regimen, the results achieved were not only substantially improved, but better than those achieved with blood and bone marrow transplant.2-10 Comparisons of similar aged patients treated using pediatric vs adult protocols are shown for the first 5 countries listed in Table 1. In France, 15- to 20-year-old patients treated using the pediatric FRALLE-93 protocol had complete remission induction of 94% and a 5-year event-free survival (EFS) of 67% compared with 83% and 41%, respectively (P = .04 and <.0001), using the adult LALA-94 protocol. In the United States, 16- to 20-year-old patients had a superior 7-year EFS of 63% on Children’s Cancer Group (CCG) trials compared with 34% on Cancer and Leukemia Group B trials (P < .05). In subsequent trials, CCG investigators reported a 5-year EFS of 71.5% for patients aged 16 to 21 years. In the United Kingdom, 15- to 17-year olds had a 5-year EFS of 65% on the pediatric ALL87 trial but only 49% using the adult UKALLXII/E2993 regimen (P = .01). In The Netherlands, 15- to 18-year olds had a 5-year overall survival of 79% and 38% using pediatric and adult study group treatment regimens, respectively. Analogous differences between pediatric and adult treatment regimens in adolescent and young adult ALL patients have been reported from Sweden, Mexico, and a third group in France (references available upon request).

In addition, when adult study groups have used pediatric-inspired therapy, improvements in outcome have been noted. In Spain, 14- to 18-year olds treated using a pediatric-inspired protocol by the adult consortium had a 2-year overall survival of 71%. In addition, a comparison of patients treated by the pediatric and adult study groups in Finland revealed a 5-year EFS of 67% and 60%, respectively, a difference that was not statistically significant.11 Of note, the Finnish Leukemia Group utilizes therapy that is similar to the pediatric Nordic (NOPHO) study group in Finland, illustrating the benefit of evolving toward pediatric-inspired therapy.

By limiting their control studies to those that used chemotherapy regimens derived from prior adult studies, Gupta and colleagues may be correct in concluding that blood and bone marrow transplant is superior to chemotherapy alone. However, at least for adults up to the age of 40 or 50 years, the appropriate comparator has become the pediatric-inspired regimen. Therefore, we stress that the more appropriate conclusion to be drawn is the importance of using more effective, conventional, pediatric-inspired ALL treatment regimens in the adolescent and young adult population, rather than the clearly suboptimal regimens historically used for adults. Barrig other specific risk factors portending a poor prognosis, when pediatric-based therapy is used for this population, the case for using blood and bone marrow transplant in first remission is far less compelling.

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References


Table 1. Outcomes for adolescent and young adult patients treated with pediatric-based vs adult-based treatment protocols

<table>
<thead>
<tr>
<th>Country</th>
<th>Clinical trials, pediatric/adult</th>
<th>Age range, y</th>
<th>Survival: E or D</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Statesa‡</td>
<td>CCG/CALGB†</td>
<td>16-21</td>
<td>E: 63% at 7 y</td>
<td>67%/46% at 7 y</td>
</tr>
<tr>
<td>United Statesb‡</td>
<td>CCG100 series</td>
<td>16-21</td>
<td>E: 72% at 5 y</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>FRALLE93LALA94†</td>
<td>15-20</td>
<td>D: 68% at 6 y</td>
<td>78% at 6 y/45%</td>
</tr>
<tr>
<td>France†</td>
<td>GGRAALL 2003</td>
<td>15-60</td>
<td>E: 55% at 4 y</td>
<td>58% at 4 y</td>
</tr>
<tr>
<td>Great Britain5</td>
<td>ALL97E/UKALLX1†</td>
<td>15-17</td>
<td>E: 65%</td>
<td>71% at 5 y/56%</td>
</tr>
<tr>
<td>United Kingdom†</td>
<td>MRC UKALLX, Xa/</td>
<td>15-20</td>
<td>D: 35% at 5 y</td>
<td>60% at 5 y</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>DCGO1HOVON†</td>
<td>15-18</td>
<td>E: 69% at 5 y</td>
<td>79% at 5 y/38%</td>
</tr>
<tr>
<td>Spain‡</td>
<td>ALL96</td>
<td>14-18</td>
<td>E: 34% at 5 y</td>
<td>71% at 2 y</td>
</tr>
<tr>
<td>Italyb‡</td>
<td>AIEOP ALL95, 2000/</td>
<td>14-18</td>
<td></td>
<td>80% at 2 y</td>
</tr>
</tbody>
</table>

D, disease-free survival; E, event-free survival.
‡Pediatric oncology organization.
†Adult oncology organization.

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Response

Chemotherapy versus allogeneic transplantation in adult patients with acute lymphoblastic leukemia in first remission: not a time for dogma

Isakoff and colleagues highlight in their letter that young adults with acute lymphoblastic leukemia (ALL) treated with a pediatric-inspired regimen do not need a bone marrow transplant in first remission. Their assumption is based on comparisons of published outcomes of young patients with ALL treated with adult and pediatric-inspired regimens mainly in the age group of 15 to 20 years. Although the outcomes of pediatric-inspired regimens in young adults 15 to 20 years old with ALL are encouraging, several factors should be taken into consideration before any valid conclusions can be drawn.

In our report, a young adult is defined as <35 years old.1 It is highly speculative that the findings of patients treated in the age group of 15 to 20 years can be generalized to those >20 years old.

The best chemotherapy regimen for young adults with ALL is unknown. A pediatric-inspired regimen may be better than a standard adult regimen, but comparison of these regimens has never been prospectively studied. One has to question the real causes of differences in outcomes with these regimens. There are minimal data on the comparison of drug dosages delivered in pediatric- vs adult-type regimens.2 Is it truly the impact of intensity of a pediatric-inspired regimen or a pediatric culture of maintaining a prescribed dosage and schedule strictly with minimal interruptions?3 In addition to these physician practice patterns, the issue is further confounded by referral patterns and patient compliance.

In summary, we present an individual patient data meta-analysis according to a well-defined study protocol (available at: http://www.ctsu.ox.ac.uk/research/meta-trials/leukaemia-metanaalyses/protocol-2009). Of course, we agree that if the outcomes of chemotherapy improve (in the absence of a concomitant improvement in the transplant), this could abrogate the need for a transplant, but we wish to emphasize that this needs to be demonstrated in prospective randomized studies, which, to our knowledge, have not yet been done. The key to the future would seem to be continued study of modern chemotherapy protocols vs allogeneic transplantation as part of well-designed prospective studies.

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References


To the editor:

Coordinate expression of transcripts and proteins in platelets

Published reports have demonstrated coordinate expression between messenger RNA and proteins in platelets.1-3 It was therefore surprising that, comparing our RNA-seq data set1 to their quantitative proteomics data set, Burkhart et al5 concluded that “in platelets, the occurrence of proteins is not interrelated to the presence of transcripts.” The accompanying highlight article reiterated that “the protein profile
Young adults with acute lymphoblastic leukemia treated with a pediatric-inspired regimen do not need a bone marrow transplant in first remission

Michael S. Isakoff, David R. Freyer and Archie Bleyer