to be due to recovery of the fucosylated unit and therefore expected dominance of the manipulated unit. It is possible that the chimerism was transient and measurements were made too late, or that the fucosylated unit served to facilitate engraftment of the fucosylated and nonfucosylated HSPCs.

This study represents an important advancement in the field of UCB transplant. The strategy used is appealing because it is simple and could be performed in any institution with a cell manipulation laboratory. Previous cell expansion studies have shown similar improvements in engraftment but require complex and time-consuming manipulations in a good manufacturing practice facility. More rapid engraftment will be expected to reduce later infections, and perhaps reduce mortality, but these key end points require a larger study.

Although an important advancement, this is an early-phase study of 22 patients, so future larger randomized studies will be needed to confirm these results in a larger data set and explore the mechanism of enhancement of engraftment. The technology use in this strategy appears simpler and more suited to a multicenter study than many approaches and could be performed in any institution.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


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CLINICAL TRIALS AND OBSERVATIONS

Comment on Brown et al, page 2915

Targeted drugs in concert with chemo: opposites attract

Clemens-Martin Wendtner1,2 and Kirsten Fischer2

In this issue of Blood, Brown and colleagues show an impressive additional value when combining a tyrosine kinase inhibitor, that is, the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, with classic chemoimmunotherapy in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma.

The combination of ibrutinib with bendamustine plus rituximab was well tolerated with no significantly added toxicity reported and induced responses in up to 97% of patients, including a complete remission in 40% of individuals after a prolonged treatment period with ibrutinib.

Nowadays, the combination of chemotherapy with α-CD20 antibodies is an international treatment standard for both treatment-naive and relapsed patients with CLL. Besides the rituximab plus fludarabine and cyclophosphamide (FCR) regimen, bendamustine in combination with rituximab (BR) has become a similarly efficacious though significantly less toxic treatment option. Recently, health authorities have approved 2 targeted drugs in relapsed/refractory CLL, that is, the BTK inhibitor ibrutinib and the phosphatidylinositol 3-kinase inhibitor idelalisib, the latter in combination with rituximab. Both drugs have shown amazing responses in heavily pretreated patients with CLL often harboring a combination of several high-risk features.

Nevertheless, these small molecules have not induced complete remissions in a high proportion of patients and, more importantly, are still new kids on the block: we do not know their long-term efficacy and toxicity. The initial reports describe only a few patients developing resistance, but this phenomenon should be closely monitored on our radar screens. Therefore, efforts to aim for deep remissions in CLL, even in the relapsed setting, remain valuable because this could enable us to discontinue treatment while potentially lowering the risk of resistance. Furthermore, patients might appreciate a limited treatment period instead of a permanent intake of cancer pills reminding them daily of their malignancy. Budgetwise this could be good news for some health economics, especially in countries with limited resources in the field of medicine.

Table 1. Responses and progression-free survival (PFS) in relapsed/refractory CLL

<table>
<thead>
<tr>
<th>Response</th>
<th>BR,2</th>
<th>FCR,6</th>
<th>Ibrutinib,3</th>
<th>FCR with ibrutinib,1</th>
<th>BR-ibrutinib,1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>59</td>
<td>69.9</td>
<td>71</td>
<td>100</td>
<td>96.7†</td>
</tr>
<tr>
<td>CR, %</td>
<td>9</td>
<td>24.3</td>
<td>2.4</td>
<td>100†</td>
<td>40†</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>15.2</td>
<td>30.6</td>
<td>Not reached (at month 26, 75% were progression free)</td>
<td>Not reached</td>
<td>Not reached (at month 12, 85.9% were progression free)</td>
</tr>
</tbody>
</table>

*Includes 1 patient with partial response and lymphocytosis.†Includes extended treatment period with ibrutinib.
In the article by Brown and colleagues, the outcome for patients with relapsed/refractory CLL was shifted from a 50% overall response rate (ORR), including only 9% complete responses (CRs), to a 93.3% ORR with a CR rate of 16.7% when combining BR with ibrutinib. Including a patient with a partial response with typical ibrutinib-associated peripheral blood lymphocytosis, the ORR climbed up to 96.7% and the CR rate increased to 40% when the extended treatment phase with ibrutinib was included. Looking at the response rates for single-agent ibrutinib with an ORR of 71% and a CR rate of 2.4%, the shift to these high remission rates for the triple combination (BR-ibrutinib) is also impressive (Table 1 1-3,6). In contrast to standard chemoimmunotherapy with BR, responses were seen in all prognostic subgroups, including patients harboring del17p. Additionally, the survival data with respect to PFS for BR-ibrutinib compare favorably to BR with the median not being reached during the follow-up of ≥3 years. Data of a second cohort of patients receiving FCR in combination with ibrutinib are very incomplete in this phase 1b trial due to slow accrual of relapsed patients who were purine analog naïve and who were candidates for FCR. The treatment with BR-ibrutinib was quite well tolerated considering that the study population was rather young (median age, 62 years) and not too heavily pretreated (maximum number of prior regimens was 3). Side effects were similar to what is usually observed when the drugs are administered individually with severe neutropenia in 40% of patients being the most frequent adverse event.

Whether the high frequency of secondary malignancies (in 11 of 30 patients) observed in this phase 1b study is worrisome or just random needs to be further investigated in subsequent larger trials evaluating this combination treatment. Besides the awaited results on safety and efficacy of a randomized trial comparing BR with or without the addition of ibrutinib, it will also be of interest to study whether the triple-combination BR-ibrutinib would allow for an earlier stopping of ibrutinib compared with a continuous application of single-agent ibrutinib. Nevertheless, the trial by Brown and colleagues sets the stage for many more in order to learn more about the risks and benefits of combining 2 extremes, that is, targeted drugs and classic chemotherapy.

Eventually, we also would like to explore whether the use of improved α-CD20 antibodies and other classes of small molecules like BH3 mimetics and Mcl-1 inhibitors might even allow for the omission of the traditional partner in this wedding: that is, instead of the chemo partner a matched pair alliance with an in-house targeted mate. Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES

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LYMPHOID NEOPLASIA

Comment on Mallampati et al, page 2968

Ph+ ALL: drawing strength from a benign past

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In this issue of Blood, Mallampati et al report on the discovery of a new mechanism of tyrosine kinase inhibitor (TKI) resistance, which is mediated through TKI-mediated priming of mesenchymal stem cells (MSCs) in the bone marrow (BM).1

B-cell lineage acute lymphoblastic leukemia (ALL) cells carrying the Philadelphia chromosome (Ph+) are addicted to BCR-ABL1. Thereby, the oncogenic BCR-ABL1 kinase mimics constitutively active cytokine signaling, which promotes proliferation and survival in normal B-cell precursors. Ph+ ALL almost invariably acquires resistance to BCR-ABL1 TKIs. The mechanisms of TKI resistance are not fully understood.

MSCs in the BM niche have been implicated as enablers of transformation and drug resistance of leukemia cells in multiple ways. For instance, MSCs were identified as the main source of asparagine,2 which promote resistance against L-asparaginase in ALL treatment. Specifically in Ph+ ALL, CXCR4-CXCL12 interactions between leukemia and BM stroma cells, derived from MSCs, were identified as a major factor of TKI resistance.3 Likewise, N-cadherin and β-catenin signaling in MSCs strongly protect leukemia cells against TKIs.4 In addition, defective innervation of MSCs by sympathetic nerve fibers represents a key regulator of leukemic transformation.5 These and other defects in leukemia-associated MSCs can be transmitted to normal MSCs and contribute to a leukemia-specific niche.6 In some cases, MSCs are carriers of driver oncogenes in human ALL, eg, MLL-AP1,7 and oncogenic activation of β-catenin in MSC-derived osteoblasts alone is sufficient to drive leukemogenesis.8 Together, these observations strongly support the concept that MSC and MSC-derived cells in the BM niche are critical mediators of leukemic transformation and drug resistance in both myeloid and B-cell lineage malignancies.

Mallampati et al1 directly measured responses of MSCs, rather than responses of

BLOOD, 7 MAY 2015 • VOLUME 125, NUMBER 19
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