Ibrutinib for the Treatment of Mantle Cell Lymphoma

Alex F. Herrera and Eric D. Jacobsen

Abstract

Ibrutinib (PCI-32765)—a potent, covalent inhibitor of Bruton tyrosine kinase (BTK), an important kinase in the B-cell receptor signaling pathway—was recently approved by the FDA for the treatment of relapsed or refractory mantle cell lymphoma (MCL). The drug was granted accelerated approval based on the findings of an international, multicenter, single-arm phase II study that enrolled patients with relapsed or refractory MCL. In the study, ibrutinib (560 mg daily) was well tolerated as a single agent and resulted in an overall response rate of 68% and an estimated median response duration of 17.5 months. Ibrutinib’s response rate and duration of response compare favorably with those for other novel agents approved for the treatment of relapsed or refractory MCL, while being less toxic than most chemotherapy or chemoimmunotherapy regimens. Ibrutinib is currently being studied in combination with chemoimmunotherapy, monoclonal antibody therapy, and novel agents in both the initial and the relapsed/refractory treatment settings. We review the mechanism of action, preclinical and clinical development, and the role of ibrutinib in the context of other available treatments. Clin Cancer Res; 20(21); 5365–71. ©2014 AACR.

Introduction

In 1952, Colonel Ogden Bruton reported the case of an 8-year-old male with frequent infections, agammaglobulinemia, and lack of antibody response to vaccination treated effectively i.v. gammaglobulin. Bruton had reported the first case of X-linked agammaglobulinemia (XLA). Later demonstrated to be caused by mutations in the gene encoding Bruton tyrosine kinase (BTK), a Tec family kinase that is integral to the B-cell receptor (BCR) signaling pathway. In normal B cells, BCR activation by antigen binding causes the Src kinases, Syk and Lyn, to phosphorylate the immunoreceptor tyrosine–based activation motifs (ITAM) of the CD79A and CD79B components of the BCR. This leads to recruitment of a number of additional kinases and proteins—including BTK—that comprise the signalosome, BTK function and BCR signaling play a key role in B-cell malignancies, including mantle cell lymphoma (MCL). Enhanced or tonic BCR signaling has been demonstrated in follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and diffuse large B-cell lymphoma (DLBCL) cell lines (2–4). Genetic alterations of Syk as well as Syk and BTK protein overexpression have been observed in MCL cell lines and patient samples (5, 6). Proteomic analyses of MCL cell lines have demonstrated a relative abundance of BCR pathway phosphoproteins (7, 8). In addition, BCR downstream effector pathways seem to be important in MCL pathogenesis. Gene expression profiling studies have demonstrated upregulation of NF-kB and PI3K pathway target genes in MCL (9). The importance of BCR signaling in the pathogenesis of B-cell malignancies prompted the development of BCR pathway kinase inhibitors, including the BTK inhibitor, ibrutinib.

Pharmacology and Preclinical Development

Ibrutinib (PCI-32765) is a very potent small-molecule inhibitor of BTK (IC_{50}, 0.5 nmol/L) that forms an irreversible covalent bond at a cysteine residue in the BTK active site. Ibrutinib is orally bioavailable and has a short half-life of about 2 hours. Although the plasma half-life of ibrutinib is short, the BTK occupancy by the drug persists 24 hours after dosing (10). Ibrutinib undergoes hepatic metabolism by CYP3A and CYP2D6 to its active metabolite, resulting in drug interactions with inducers or inhibitors of CYP3A. Ibrutinib also inhibits other kinases with homologous cysteine residues, including TEC, ITK, JAK3, EGFR, HER2, HER4, BLK, and BMX (11). Off-target inhibition of these kinases may account for ibrutinib–associated toxicities.

In preclinical studies, ibrutinib disrupted downstream BCR signaling and induced apoptosis in a range of B-cell

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malignancy cell lines, including CLL, activated B-cell subtype DLBCL, Waldenstrom macroglobulinemia, and MCL (2, 3, 5, 12). In dogs with spontaneous non-Hodgkin lymphoma, treatment with ibrutinib resulted in three partial responses (PR) and stabilization of lymphoma in 3 dogs, while only 2 dogs developed progressive lymphoma. Ibrutinib induced potent \textit{in vivo} inhibition of BTK phosphorylation in the treated dogs (13).

**Clinical Development**

On the basis of these promising preclinical findings, a multicenter phase 1 dose-escalation study of ibrutinib in relapsed or refractory B-cell malignancies was undertaken. Fifty-six patients with B-cell malignancies, including FL, CLL/SLL, marginal zone lymphoma, DLBCL, Waldenstrom macroglobulinemia, and MCL, were enrolled and treated either in one of five escalating dose cohorts—1.25, 2.5, 5, 8.3, or 12.5 mg/kg—for 28 consecutive days with the final 7 days off in 35-day cycles, or received fixed dose ibrutinib at either 8.3 mg/kg or 560 mg daily until disease progression, unacceptable toxicity, or study withdrawal by the investigators. Only one line of prior therapy was required for study entry, but the median number of prior therapies was three (range, 1–10) and most patients had received prior rituximab or alkylating agent therapy. The maximum tolerated dose was not reached in the study, and only two dose-limiting toxicities occurred: one dose interruption because of an episode of grade 2 neutropenia, and one episode of grade 3 drug hypersensitivity. In 50 patients evaluable for response, the overall response rate (ORR) was 60%. Responses were seen at all dose levels and in all subtypes of B-cell malignancy studied, including responses in 7 of 9 (78%) patients with MCL. Three patients with MCL had complete responses (CR), 4 had PRs, 1 patient had stable disease, and 1 patient had progressive disease. Pharmacodynamic studies reported from a representative patient demonstrated full BTK occupancy by ibrutinib throughout the treatment cycles (10).

Multiple subsequent studies of ibrutinib in CLL, FL, DLBCL, and MCL have followed the phase I trial. An international open-label phase II study was performed in patients with relapsed or refractory MCL. Patients received 560 mg of oral ibrutinib daily until disease progression or unacceptable toxicity. The primary endpoint of the study was the ORR. A total of 115 patients were enrolled in the study, and 111 patients received ibrutinib and were

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**Figure 1.** Ibrutinib inhibits BTK in the BCR pathway. BLNK, B-cell linker protein; Ca, calcium; DAG, diacylglycerol; IgH, immunoglobulin heavy chain; IgL, immunoglobulin light chain; IKK, inhibitor of NF-κB kinase; IP3, inositol-1,4,5-trisphosphate; PKC, protein kinase C; PIP2, phosphatidylinositol-4,5-biphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PLC, phospholipase C.
months (range, 1.7–11.5). The median duration of
response (DOR) was 17.5 months (range, 0.0–19.6) in
responders, and the median progression-free survival
(PFS) in the entire cohort was 13.9 months (range,
0.7–21.4). There were no baseline or disease character-
istics that were associated with response. On the
basis of the promising outcomes observed in this
single-arm phase II study, the FDA granted accelerated
approval of ibrutinib for patients with relapsed or refrac-
tory MCL who have received at least one prior regimen
(14).

There are ongoing clinical trials evaluating the addition of
ibrutinib to first-line MCL treatment and additional trials
testing combinations of ibrutinib and other medications for
treatment of relapsed or refractory MCL. Table 1 sum-
marizes the current clinical trials evaluating ibrutinib for
the treatment of MCL.

Toxicity
Ibrutinib has been well tolerated in clinical trials, with the
majority of reported adverse events being grade 1 or 2. The
most common reported adverse events were diarrhea
(46%–50%), fatigue (41%), nausea (31%–43%), decreased
appetite (21%–35%), peripheral edema (28%), dyspnea
(27%), vomiting (23%), upper respiratory tract infection
(21%), and cough (18%–32%). The most common grade 3
or 4 adverse events were neutropenia (12%–16%) and
thrombocytopenia (7%–11%). Immunoglobulin levels of
patients treated in clinical trials have been unaffected. Very
few patients treated in clinical trials have had to discontinue
treatment due to toxicity (10, 14).

Similar to patients with CLL/SLL, about one third of
patients with MCL treated with ibrutinib develop transient
lymphocytosis concurrent with a reduction in lymphade-
nopathy. Flow cytometric analysis has demonstrated that
the circulating lymphocytes coexpress CD19 and CD5, are
light chain-restricted, and are phenotypically consistent with
MCL cells. These circulating MCL cells have decreased
proliferative/activation capacity, with decreased expression of
the proliferation marker Ki-67 and decreased CD38 and
phospho-ERK expression. Treated patients who develop
lymphocytosis also seem to have decreased levels of che-
mokines that affect B-cell trafficking and homing. The
lymphocytosis generally improves after approximately 2
months of treatment and resolves by the fourth or fifth
month of treatment (15). These circulating MCL cells may
provide an attractive target for combined ibrutinib and
monoclonal antibody therapy.

Treatment of MCL
Historically, the initial treatment of MCL used combina-
tion chemoimmunotherapy such as the anti-CD20 mono-
clonal antibody, rituximab, added to cyclophosphamide,
doxorubicin, vincristine, and prednisone (R-CHOP). The
combination of bendamustine and rituximab (BR) has
increasingly supplanted R-CHOP based on a subgroup
analysis of a randomized trial demonstrating less toxicity
and superior PFS with BR (16). Young, fit patients com-
monly receive aggressive induction regimens such as ritux-
imab plus cyclophosphamide, doxorubicin, vincristine,
and dexamethasone alternating with high-dose cytarabine
and methotrexate (R-HyperCVAD) or the Nordic regimen
(high-dose R-CHOP alternating with rituximab plus high-
dose cytarabine; refs. 17, 18). Consolidation with high-dose
chemotherapy followed by autologous stem cell transplan-
tation (ASCT) is associated with prolonged disease-free
survival after conventional chemoimmunotherapy, but
not after R-HyperCVAD (19, 20). In a randomized trial
comparing R-CHOP alone with R-CHOP alternating with
rituximab plus dexamethasone, high-dose cytarabine, and
cisplatin (R-DHAP) as induction before ASCT, the inclusion
of R-DHAP was associated with prolonged overall survival.
Most experts now suggest using regimens that incorporate
cytarabine before ASCT (21). In elderly patients who are not
candidates for ASCT, rituximab maintenance after standard
chemoimmunotherapy extends overall survival compared
with IFN-α (22). The relative efficacy of rituximab mainte-
nance versus consolidation with ASCT in younger patients
remains to be defined.

Unfortunately, existing therapy for MCL is not curative.
Before the approval of ibrutinib, the range of treatment
options for relapsed or refractory disease included non-
cross-resistant chemoimmunotherapy regimens, single-
agent rituximab, or novel agents, including the proteasome
inhibitor, bortezomib, the immunomodulatory agent,
lenalidomide, and the mTOR inhibitor, temsirolimus.
Bortezomib is FDA approved for the treatment of patients with
MCL who have relapsed after receiving at least one prior
regimen. In the largest prospective phase II trials evaluating
bortezomib mostly in previously treated patients with
relapsed or refractory MCL, the ORR ranged from 33% to
47% with a CR rate ≤10%. The median duration of response
to bortezomib in these studies ranged from 8 to 10 months
(23–25). Lenalidomide is also FDA approved for the treat-
ment of MCL in patients who have received two or more
prior therapies, including bortezomib. About one third of
patients respond to lenalidomide, with the CR rate generally
≤10%, though the median DOR is longer than that of
bortezomib at roughly 17 months (26). Temsirolimus is
approved by the European Medicines Agency for the
treatment of relapsed or refractory MCL based on the results of a randomized phase III trial demonstrating a higher response rate and PFS to temsirolimus than to investigator’s choice therapy (27). The FDA has not approved the drug for this indication. Table 2 summarizes the findings of selected studies of these novel agents in the treatment of relapsed or refractory MCL. Although randomized trials are lacking, ibrutinib seems to have superior efficacy to all of these agents.

When to Use Ibrutinib

The important question that remains to be answered is, where will ibrutinib ultimately fit in the treatment of MCL? Currently, ibrutinib is not approved for the initial treatment of MCL. First-line combination chemoimmunotherapy remains the standard of care for the initial treatment of MCL. Candidates for ASCT should be referred for consideration of consolidative ASCT after initial treatment as this approach has demonstrated the most durable remissions. Recent data suggest that high-dose cytarabine should be incorporated into the initial treatment regimen, if it can be tolerated, in patients who are candidates for consolidative ASCT. For patients who are not candidates for ASCT, maintenance rituximab after initial chemoimmunotherapy is a reasonable option.

Patients who relapse after ASCT or who relapse after initial therapy and are not candidates for ASCT are ideal candidates for single-agent ibrutinib therapy. Although these two regimens have never been directly compared, we prefer the use of ibrutinib in this setting to the other novel agents because of its ease of administration, favorable

### Table 1. Current clinical trials of ibrutinib in MCL

<table>
<thead>
<tr>
<th>Phase/design</th>
<th>Population</th>
<th>Design</th>
<th>Agents</th>
<th>Primary endpoint</th>
<th>Location</th>
<th>CT.gov ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>R/R B-NHL</td>
<td>Dose-escalation</td>
<td>Ibrutinib + lenalidomide</td>
<td>MTD</td>
<td>OSU</td>
<td>NCT01955499</td>
</tr>
<tr>
<td>Phase I</td>
<td>HIV+ with R/R B-NHL</td>
<td>Dose-escalation</td>
<td>Ibrutinib</td>
<td>MTD</td>
<td>MSKCC</td>
<td>NCT02109224</td>
</tr>
<tr>
<td>Phase I</td>
<td>Relapsed iNHL</td>
<td>Dose-escalation</td>
<td>BR + ibrutinib</td>
<td>MTD</td>
<td>OSU</td>
<td>NCT01479842</td>
</tr>
<tr>
<td>Phase I</td>
<td>Previously treated MCL</td>
<td>Dose-escalation</td>
<td>Ibrutinib + palbociclib isethionate</td>
<td>RP2D</td>
<td>Cornell</td>
<td>NCT02159755</td>
</tr>
<tr>
<td>Phase Ib</td>
<td>Upfront B-NHL</td>
<td>Dose-escalation</td>
<td>Ibrutinib + R-CHOP</td>
<td>MTD</td>
<td>United States France</td>
<td>NCT01569750</td>
</tr>
<tr>
<td>Phase Ib</td>
<td>Relapsed B-NHL, expansion upfront MCL</td>
<td>Dose-escalation</td>
<td>Ibrutinib + R-DHAP or R-DHAOx</td>
<td>RP2D, DLT</td>
<td>Belgium France</td>
<td>NCT02055924</td>
</tr>
<tr>
<td>Phase II</td>
<td>R/R MCL, failed ≥ 1 therapy</td>
<td>Single-arm (multicenter)</td>
<td>Ibrutinib + ublituximab</td>
<td>Safety</td>
<td>United States</td>
<td>NCT02013128</td>
</tr>
<tr>
<td>Phase II</td>
<td>Relapsed B-NHL</td>
<td>Single-arm (multicenter)</td>
<td>Ibrutinib</td>
<td>Safety</td>
<td>United States</td>
<td>NCT01109069</td>
</tr>
<tr>
<td>Phase II</td>
<td>R/R MCL</td>
<td>Single-arm (single-center)</td>
<td>Ibrutinib + rituximab</td>
<td>ORR</td>
<td>MDACC</td>
<td>NCT01880567</td>
</tr>
<tr>
<td>Phase II</td>
<td>R/R MCL</td>
<td>Single-arm (multicenter)</td>
<td>Ibrutinib alone</td>
<td>ORR</td>
<td>Japan</td>
<td>NCT02169180</td>
</tr>
<tr>
<td>Phase II</td>
<td>Relapsed MCL, progressed after bortezomib</td>
<td>Single-arm (multicenter)</td>
<td>Ibrutinib alone</td>
<td>ORR</td>
<td>International</td>
<td>NCT01599949</td>
</tr>
<tr>
<td>Phase III</td>
<td>R/R MCL, failed ≥ 1 therapy</td>
<td>Randomized (multicenter)</td>
<td>Ibrutinib vs. temsirolimus</td>
<td>PFS</td>
<td>International except U.S.</td>
<td>NCT01646021</td>
</tr>
<tr>
<td>Phase III</td>
<td>First-line MCL</td>
<td>Randomized, double-blind, placebo-controlled (multicenter)</td>
<td>BR ± ibrutinib</td>
<td>PFS</td>
<td>International</td>
<td>NCT01776840</td>
</tr>
</tbody>
</table>

Abbreviations: B-NHL, B-cell non-Hodgkin lymphoma; DLT, dose-limiting toxicity; iNHL, indolent non-Hodgkin lymphoma; JHU, Johns Hopkins University (Baltimore, MD); MDACC, University of Texas MD Anderson Cancer Center (Houston, TX); MSKCC, Memorial Sloan Kettering Cancer Center (New York, NY); MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; OSU, Ohio State University (Columbus, OH); PrinMarg, Princess Margaret Hospital (Toronto, ON, Canada); R-DHAOx, rituximab, dexamethasone, high-dose cytarabine, oxaliplatin; RP2D, recommended phase II dose; R/R, relapsed/refractory; UChicago, University of Chicago (Chicago, IL).
toxicity profile, and higher response rate. In comparison, bortezomib produces fewer and shorter responses, requires more frequent visits for administration, and is associated with hematologic toxicity and peripheral neuropathy. Although lenalidomide offers the convenience of an oral medication, the reported response rates are substantially lower and the reported rates of hematologic toxicity are higher than those of ibrutinib. Temsirolimus is not

<table>
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<tr>
<th>Age in years (range)</th>
<th>Median no. prior regimens (range)</th>
<th>Dose</th>
<th>Response rate</th>
<th>Median duration of response/PFS</th>
<th>Survival</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Ibrutinib</strong></td>
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<tr>
<td>9</td>
<td>65 (41–82)</td>
<td>Phase I dose-escalation or fixed dose of 8.3 mg/kg or 560 mg daily</td>
<td>78% ORR</td>
<td>13.6 mo PFS</td>
<td>Not reported</td>
<td>Advani et al. (10)</td>
</tr>
<tr>
<td>111</td>
<td>68 (40–84)</td>
<td>560 mg daily</td>
<td>68% ORR</td>
<td>17.5 mo DOR</td>
<td>OS 58% (18 mo)</td>
<td>Wang et al. (14)</td>
</tr>
<tr>
<td><strong>Bortezomib</strong></td>
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<tr>
<td>155</td>
<td>67 (30–86)</td>
<td>1.3 mg/m² d1, 4, 8, 11; 21-d cycle</td>
<td>33% ORR</td>
<td>9.2 mo DOR</td>
<td>OS 69% (1 y)</td>
<td>Fisher et al. (23)</td>
</tr>
<tr>
<td>40</td>
<td>67.5 (45–83)</td>
<td>1.5 mg/m² d1, 4, 8, 11; 21-d cycle</td>
<td>47% ORR</td>
<td>5.3 mo PFS</td>
<td>—</td>
<td>O’Connor et al. (25)</td>
</tr>
<tr>
<td>30</td>
<td>67 (48–79)</td>
<td>1.3 mg/m² d1, 4, 8, 11; 21-d cycle</td>
<td>46% ORR</td>
<td>10 mo DOR</td>
<td>—</td>
<td>Belch et al. (24)</td>
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<tr>
<td><strong>Lenalidomide</strong></td>
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<tr>
<td>134</td>
<td>67 (43–83)</td>
<td>25 mg daily d1–21; 28-d cycles</td>
<td>28% ORR</td>
<td>16.6 mo DOR</td>
<td>OS 19.0 mo (median)</td>
<td>Goy et al. (26)</td>
</tr>
<tr>
<td>57</td>
<td>68 (33–82)</td>
<td>25 mg daily d1–21; 28-d cycles</td>
<td>35% ORR</td>
<td>16.3 mo DOR</td>
<td>—</td>
<td>Zinzani et al. (33)</td>
</tr>
<tr>
<td>26</td>
<td>66 (45–81)</td>
<td>25 mg daily d1–21; 28-d cycles; 15 mg maintenance (responders)</td>
<td>31% ORR</td>
<td>22.2 mo DOR</td>
<td>OS 10.0 mo (median)</td>
<td>Eve et al. (34)</td>
</tr>
<tr>
<td><strong>Temsirolimus (175/75-mg dosing arm only)</strong></td>
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<tr>
<td>54</td>
<td>68 (44–87)</td>
<td>175 mg weekly x 3 wks, then 75 mg weekly</td>
<td>22% ORR</td>
<td>7.1 mo DOR</td>
<td>OS 11.1 mo (median)</td>
<td>Hess et al. (27)</td>
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</tbody>
</table>

Abbreviations: CRu, unconfirmed CR; DOR, duration of response; OS, overall survival; SD, stable disease.
approved to treat MCL in the United States, requires i.v. administration, and has a lower reported response rate than that of ibrutinib.

Conclusions and Future Directions

Ibrutinib is a potent covalent inhibitor of BTK, an essential component of the BCR signaling pathway, with activity across a range of B-cell malignancies. Ibrutinib has been approved for the treatment of patients with relapsed or refractory MCL who have received at least one prior regimen. However, while ibrutinib is effective for many patients with relapsed or refractory disease, a substantial minority of patients do not respond and there is no evidence that the drug cures MCL. Experiments in MCL cell lines demonstrated that cell lines sensitive to ibrutinib displayed chronic activation of the NF-κB pathway, whereas insensitive cell lines exhibited alternative NF-κB signaling (28). In the future, predictive biomarkers may be available in the clinic that would allow clinicians to select patients most likely to benefit from ibrutinib therapy. Ibrutinib resistance is under study and mechanisms of resistance to ibrutinib have been identified—for example, a C481S mutation in BTK interrupts covalent but noncovalent binding of ibrutinib to its target; and treatments to overcome resistance, including epigenetic modification, may emerge (11, 29).

Other BTK inhibitors, such as AVL-292/CC-292, ACP-196, HM-71224, and ONO-4059, are under development. Many of these newer agents have higher BTK specificity and binding affinity than ibrutinib, though the clinical impact of these pharmacologic properties remains unclear. In addition to BTK inhibitors, other promising agents in development for the treatment of MCL include the BH3-mimetic, ABT-199, and the PI3K inhibitor, idelalisib. Interim results of a phase I dose-escalation study of ABT-199 in relapsed/refractory non-Hodgkin lymphomas, including MCL, showed that 9 of 9 patients enrolled with MCL had a PR (30). Given the role that the BCR and downstream PI3K pathways have in the pathogenesis of MCL and other B-cell malignancies, therapeutic PI3K inhibition is an attractive approach. In a phase I dose-escalation study of idelalisib in heavily pretreated patients with relapsed/refractory MCL, 16 of 40 (40%) patients had an objective response, with two CRs. The median DOR was 2.7 months, and the 1-year PFS rate was 22% (31).

Although the role of ibrutinib is currently limited to use as a single agent in the relapsed/refractory setting, because of its favorable toxicity profile, it is an attractive agent to consider for studies in other settings. Ongoing trials are combining ibrutinib with chemoimmunotherapy for the initial treatment of MCL and for the treatment of relapsed/refractory MCL. Ibrutinib is also being combined with rituximab or such novel agents as lenalidomide for patients with relapsed/refractory MCL. Concurrent exposure of MCL cell lines to ibrutinib and bortezomib, including cell lines resistant to bortezomib, resulted in synergistic cell killing and NF-κB inhibition (32). Thus, dual proteasome and BTK inhibition may be an attractive combination for evaluation in future clinical trials. Other options that may be considered for study include ibrutinib maintenance after initial therapy in patients with MCL who are not ASCT candidates or maintenance after autologous or allogeneic stem cell transplantation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: A.F. Herrera
Writing, review, and/or revision of the manuscript: A.F. Herrera, E.D. Jacobsen

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