

# A Summer of Change in Hematologic Malignancies: Highlights in B-Cell Malignancies From the 2013 ASCO, EHA, and ICML Meetings

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In only 2 years, the therapeutic world in hematologic malignancies has totally spun off its axis into another galaxy, at least for lymphomas and chronic lymphocytic leukemia (CLL). Nearly gone are strategies based on conventional, cytotoxic chemotherapeutic agents; indeed, there are really none still in development. The period of ennui in which one acronym was compared with another or the same regimen was given by different schedules has gone Neolithic. What we are seeing now is a proliferation of novel agents that either target the cell surface, such as monoclonal antibodies and antibody-drug conjugates, or affect the tumor microenvironment, such as immunomodulatory and PD-1/PD-L1 targeting agents, with most attention focused on those that interfere with intracellular signaling mechanisms. Instead of drugs that are intravenous and nonspecific, and that result in alopecia, mucositis, and other unpleasanties, many of the new drugs are oral and well tolerated. These are the topics that captivated our attention at the American Society of Clinical Oncology (ASCO) meeting, the European Hematology Association (EHA) congress, and the International Conference on Malignant Lymphoma (ICML), all in June.

Indeed, as recently as September 2009, Elizabeth Ashforth and I produced a supplement for *Clinical Advances* from ASCO, EHA, and the Pan Pacific Lymphoma Conference.<sup>1</sup> The presentations considered novel for that time included bendamustine in CLL,<sup>2</sup> R-CHOP-14 vs R-CHOP-21 in diffuse large B-cell lymphoma,<sup>3</sup> and the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study comparing 2 chemotherapy regimens for autologous stem cell transplantation.<sup>4</sup> However, there was the appearance of lenalidomide for non-Hodgkin lymphoma,<sup>5</sup> and brentuximab vedotin for Hodgkin lymphoma,<sup>6</sup> heralding the new era.

Several reports from the recent June meetings kindled interest in the PI3-kinase inhibitors, alone and in combination with rituximab and bendamustine. Idelalisib, which targets the  $\delta$  isoform of PI3-kinase,

achieved responses in almost 60% of patients with previously treated CLL, including those with P53 mutations.<sup>7</sup> Toxicities primarily include infections, diarrhea, and transaminitis. In relapsed/refractory CLL patients, idelalisib achieved response rates of 89% when combined with rituximab, 78% when combined with bendamustine, and 87% when combined with both agents.<sup>8</sup> About half of patients with relapsed/refractory indolent NHL, including those resistant to bendamustine and rituximab, achieved higher response rates when the drug was delivered at the full occupancy doses.<sup>9</sup> Idelalisib had a favorable safety profile. Salles and coworkers enrolled 125 patients with indolent NHL onto a phase 2 trial of single-agent idelalisib.<sup>10</sup> An interim analysis showed a notable response rate of 53.6%, which included patients who were considered refractory to both rituximab and bendamustine.<sup>10</sup> The median progression-free survival was 11.4 months.<sup>10</sup> The combination with rituximab was also explored in treatment-naïve patients ages 65 years and older with CLL/small lymphocytic lymphoma.<sup>11</sup> For the 64 patients, who were a median age of 71 years, the overall response rate was an impressive 97%, which included hematologic responses in all patients with thrombocytopenia and anemia. In patients with relapsed/refractory indolent NHL, combinations of idelalisib plus rituximab, bendamustine, or both achieved responses in approximately 80% of patients with comparable durability, suggesting that the age of a chemo-free paradigm is on the horizon.<sup>12</sup> Hopefully, this possibility will be supported by an ongoing, randomized comparison in previously treated indolent NHL of rituximab plus either idelalisib or placebo. Limited activity was reported in relapsed and refractory Hodgkin lymphoma, with an overall response rate of 12%.<sup>13</sup>

Ibrutinib is a Bruton's tyrosine kinase inhibitor that was shown to be exquisitely active in CLL. In the relapsed/refractory setting, 50% to 60% of patients responded, including those with adverse features, and,

notably, in the frontline setting in elderly patients, more than 90% experienced benefit, including those with the previously intractable 17p deletion.<sup>14</sup> Responses, mostly partial, occurred quickly and appeared to be durable. The trade-off was some fatigue, diarrhea, rash, transaminitis, and cytopenias, occasionally with accompanying infections. What we saw was that adverse prognostic factors are only relevant until you have the proper therapies to overcome them. This agent is also being explored in other lymphoma histologies, achieving results in mantle cell lymphoma,<sup>15</sup> the activated B-cell subset of diffuse large B-cell non-Hodgkin lymphoma (NHL),<sup>16</sup> and even Hodgkin lymphoma (HL), where modest activity was reported in a small series of heavily pretreated patients.<sup>17</sup>

Additional agents with promise include the PI3-kinase,  $\delta/\gamma$  inhibitor IPI-145, and ABT-199, a specific inhibitor of BCL-2.<sup>18,19</sup> Additional PI3k, BTK, and spleen-tyrosine kinase (Syk) inhibitors are also in development alone and in various combinations.

Because of the astounding success of rituximab in the treatment of B-cell malignancies, about a dozen anti-CD20s have been evaluated in clinical trials. Ublituximab was recently shown to achieve responses in more than 60% of a small series of patients with relapsed CLL.<sup>20</sup> The combination of idelalisib and ofatumumab has also provided interesting results. However, for a new anti-CD20 to displace rituximab, it would need to be more active in a direct comparison or active in patients clearly resistant to rituximab. The latter has not yet been demonstrated in CLL or NHL, nor has the former criterion yet been achieved in follicular NHL. However, a preliminary analysis of the randomized CLL11 trial presented at ASCO suggests that chlorambucil combined with either rituximab or obinutuzumab is superior to chlorambucil alone, and that the latter combination may be associated with a higher response rate than the rituximab combination.<sup>21</sup> A more complete analysis and longer follow-up of this study are needed to confirm these promising findings.

How best to evaluate these new agents was a topic of a workshop and presentation at ICML.<sup>22</sup> Staging and response criteria were initially developed for HL more than 60 years ago, but not until 1999 were response criteria by an International Working Group published for NHL.<sup>23</sup> Revisions to these criteria for both NHL and HL were published in 2007 by the International Harmonization Project on Lymphoma.<sup>24</sup> These guidelines, which incorporated positron emission tomography (PET) for response assessment, were widely adopted. After years of experience, new preliminary recommendations to improve on the International Working Group criteria included that PET-computed tomography (CT) should be used to stage fluorodeoxyglucose (FDG)-avid lymphomas; for

others, CT will define stage.<sup>22</sup> Whereas Ann Arbor classification will still be used for disease localization, patients may be grouped into Limited Disease (I(E), II(E)), and Extensive Disease (III-IV(E)) for treatment purposes, as appropriate, recognizing that stages I and II may be treated differently in certain histologic subtypes. A and B designations need only be applied to the limited clinical situations where they impact treatment (eg, stage II HL). PET-CT can replace the bone marrow biopsy for HL. A positive PET of bone or bone marrow is adequate to designate advanced stage in diffuse large B-cell lymphoma (DLBCL). However, bone marrow biopsy (BMBx) can be considered in DLBCL patients with no PET evidence of bone marrow involvement, if identification of discordant histology is relevant for patient management, or if the results would alter treatment. BMBx remains recommended for staging of other histologies. PET-CT will be used to assess response in FDG-avid histologies using the 5-point Deauville scale, but CT will be used for nonavid histologies. Currently, bidimensional measurement for response and progressive disease will be retained; however, the possibility of unidimensional measurements is being explored. Routine surveillance scans were discouraged, and the number of scans should be minimized in practice and in clinical trials. Publication of the final recommendations is eagerly anticipated.

Clearly, multiple myeloma and, more so, the acute leukemias, have lagged behind lymphoma and CLL. The myeloma studies this summer continued to focus on high-dose chemotherapy with various lenalidomide strategies. Some promise was offered by positive data with pomalidomide in patients who had failed lenalidomide and bortezomib.<sup>25</sup> Hopefully, other effective, novel, targeted agents will be identified in the foreseeable future.

As excited as we are about this proliferation of new agents, caution will have to be exercised. They are likely to be extremely expensive and, as currently used, will require continuous administration until progressive disease, prohibitive toxicity, or inability to afford them. Thus, it is incumbent upon clinical researchers to identify pretreatment biological characteristics that reliably distinguish those patients most likely to respond to one agent or another, and to discover the mechanisms by which some patients either present with resistant disease or acquire resistance with continued drug administration. For example, using genomic analysis, rare mutations have been identified in CLL, diffuse large B-cell NHL, and mantle cell lymphoma associated with resistance to ibrutinib. Additional studies are critically needed.

The studies presented demonstrated that, while highly effective and well tolerated, these agents are not curative and, indeed, mostly induce partial, albeit often durable, responses. Patients and their physicians have

long dreamed of a chemo-free approach to lymphoma and CLL. That we finally have the tools to realize this goal is certainly apparent from these June presentations. The obvious tendency will be to combine them to achieve even greater benefit, an objective, however, that must be guided by sound scientific rationale.

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