Lessons From ASH 2010: A Focus on NHL

At the 52nd Annual Meeting and Exposition of ASH in December, some 881 abstracts included information on Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL), with at least 363 on chronic lymphocytic leukemia (CLL). This brief summary discusses some of the important findings that will begin to impact practice.

Follicular Lymphoma

Overall survival (OS) for patients with follicular lymphoma (FL) has improved since the introduction of rituximab. Data have shown that for patients who need treatment, rituximab added to chemotherapy improves overall response (OR) and complete response (CR) rates, progression-free survival (PFS), and OS.1–4

In an update of the Primary Rituximab and MAintenance (PRIMA) trial, Salles et al.5 enrolled patients with untreated, high tumor-burden FL. Patients were treated with 1 of 3 regimens (R-CHOP, R-CVP, or R-FCM) at the discretion of the treating physician. Patients with a partial response or CR were randomized to observation or maintenance with rituximab, 375 mg/m², once every 8 weeks for 2 years. At a median of 42 months after registration, the 36-month PFS was 75% in the maintenance arm versus 58% in the observation arm, which met the primary end point of a 45% improvement in median PFS. The only safety issue was a slight increase in risk of infection in the maintenance group.

In a subanalysis of the PRIMA study, Trotman et al.6 examined the role of FDG-PET imaging to predict outcome in FL. At diagnosis, 99% (119/120) of PET scans were positive, demonstrating their utility for initial diagnosis. Among 124 patients who underwent PET scans after completion of induction chemotherapy, patient characteristics were similar to those of the entire study population. Discordance was noted between response assessments determined by CT and PET. The post-induction PET was shown to be a better discriminator of outcome than the CT scan. At 3 years, patients with a positive PET scan had significantly inferior PFS (32% vs. 74%) and OS (88% vs. 97%). These findings showed that the updated Cheson response criteria, which include FDG-PET, are applicable to patients with FL.

The updated results of the FIT trial,7 which examined consolidation with ⁹⁰Y-ibrituomab tiuxetan radioimmunotherapy (RIT) after initial (immuno) chemotherapy for FL, were similar to those already published but provided more information about patients initially treated with rituximab-based therapy. Among those patient the CR and CR-unconfirmed (CRu) was improved with RIT consolidation. A higher risk of secondary myelodysplastic syndromes (MDS)/acute myeloid leukemia in the RIT consolidation arm was concerning, but the difference was not quite statistically significant. Nonetheless, RIT consolidation provided a 3-year prolongation of PFS compared with observation. Available data do not directly address the choice between consolidation with RIT or maintenance with rituximab, but both represent options to prolong PFS. Neither post-remission strategy has been shown to improve OS.

Given the favorable impact of rituximab on OS in patients with FL, an international cooperative effort reexamined the role of observation in patients with low tumor burden.8 The trial objective was to determine if treatment with rituximab in asymptomatic advanced-stage FL significantly delayed chemotherapy or radiotherapy compared with observation. Patients were initially randomized to observation, rituximab weekly for 4 weeks, or rituximab weekly for 4 weeks followed...
by rituximab maintenance, but an early analysis led to the closure of the second arm. At a median follow-up of 32 months, a significant difference was seen in the initiation of new therapy among the arms (44%, 23%, and 10%, respectively), which translated to significant differences in PFS in a pair-wise comparison. However, no difference was seen in OS. The major critique of this study is the primary end point of starting new therapy. This benefit may be important if sustained impact on quality of life is seen, but the analysis is still pending. Although OS is the ultimate end point, time to the start of second therapy would provide a more balanced assessment among the study arms.

This study left many physicians wondering how to select patients for observation, and an interesting preliminary report may shed light on this dilemma. A study by Kedmi et al. used a quantitative image analysis to determine the intrafollicular proliferative index (PI) and correlated the PI to outcome. The median PI was found to be 28%, and therefore a cutoff of 30% was used to analyze outcome. Among patients with asymptomatic low tumor-burden FL who were initially observed, those with a PI of 30% or less had a median time to start of therapy of approximately 5 years, compared with 18 months for patients with a PI greater than 30%. If these findings are confirmed in an independent dataset, intrafollicular PI may be a valuable tool in selecting patients for observation.

In a randomized prospective trial, Coiffer et al. randomized 676 patients with relapsed or progressive FL to treatment with either bortezomib (1.6 mg/m² on days 1, 8, 15, 22, cycles 1–5) and rituximab (375 mg/m² on days 1, 8, 15, 22 of cycle 1 and day 1 of cycles 2–5) or rituximab alone on the same schedule. At a median follow-up of 34 months, median PFS was 11 months in the rituximab-alone arm versus 13 months in the rituximab/bortezomib arm. A 5.4-month difference was seen in time to next therapy. Although this difference is statistically significant, the clinical benefit of rituximab/bortezomib is unclear, and significantly greater neurotoxicity was seen (17% vs. 1%).

Mantle Cell Lymphoma

In a prospective trial, Hermine et al. randomized 497 patients with mantle cell lymphoma (MCL) to induction therapy with either R-CHOP or alternating R-CHOP/R-DHAP before high-dose therapy with autologous stem cell rescue (HDT/ASCR). The CR/CRu rate was significantly higher in the alternating arm after induction, but this difference was lost after HDT/ASCR. Time to treatment failure favored the alternating arm. No difference in OS was seen at a median follow-up of 32 months. This trial showed that inclusion of cytarabine in the induction regimen for MCL improved time to treatment failure, but further follow-up is needed to determine impact on OS.

Aggressive B-Cell Lymphoma

Primary mediastinal B-cell lymphoma (PMBL) represents a unique entity in malignant lymphomas. Morphologically, it is strikingly similar to diffuse large B-cell lymphoma; however, gene expression profiling shows that it more closely resembles HL. Because PMBL is often seen in young women, eliminating radiation therapy potentially reduces risk for late complications. In an analysis of 54 patients (56% women) with PMBL treated with sequential R-CHOP followed by ICE with no radiation therapy, 5-year PFS was 78% and OS was 88%. Bulky disease did not impact outcomes. Interim FDG-PET after R-CHOP did not predict for PFS. One patient developed MDS and 10 experienced relapse, of whom 6 underwent HDT/ASCR and 5 remain progression-free. These data show that patients with PMBL can have an excellent outcome without radiation therapy.

Hodgkin Lymphoma

The early favorable results of the Stanford V radiochemotherapy regimen for HL led to a U.S. Intergroup comparison of ABVD chemotherapy and Stanford V radiochemotherapy. In this study, Gordon et al. randomized 812 patients to either ABVD, with involved-field radiation (IFRT) given only to those with massive mediastinal disease, or the Stanford V regimen (12 weeks of chemotherapy), followed by IFRT only given to those with nodal sites larger than 5 cm in transverse dimension, to determine if the Stanford V regimen would result in a 33% reduction in failure-free survival (FFS) hazard rate. The study was well balanced for the major prognostic factors, including International Prognostic Score (IPS).

In this study, 40% of patients on the ABVD arm received radiation therapy compared with 73% on the Stanford V arm. No statistically significant difference was seen in response rate. The 5-year FFS was 73% for ABVD and 71% for Stanford V. In a subset of patients with IPS of 3 or greater, ABVD showed a significant advantage in 5-year FFS (68% vs. 58%). Toxicity was similar in the arms, although more lymphopenia and neuropathy were seen in patients on the Stanford V regimen.

In a subset analysis of this study involving 237 patients with bulky mediastinal stage I/II disease who had received 36 Gy IFRT to the mediastinum, bilateral supraclavicular, and hila, Advani et al. found no significant difference in...
Brentuximab vedotin (BV) is an antibody drug conjugate that targets the antitubulin agent monomethyl auristatin E (MMAE) to CD30+ cells. After endocytosis of the antibody drug conjugate, MMAE is released by intra-lysosomal protease cleavage. The primary end point of a phase II study involving patients with relapsed or refractory HL was to establish OR and CR rates for those who had previously undergone HDT/ASCR. Patients were treated with the recommended dose of BV, 1.8 mg/m², every 3 weeks for a maximum of 16 cycles (median, 9 treatments). CR was seen in 34% of patients. Remarkably, 96 of 102 patients experienced some tumor reduction. Median PFS was 25.1 weeks and median response duration was 29 weeks.

Interestingly, median PFS after BV was superior to that of the prior treatment. However, 20% of patients discontinued the drug secondary to an adverse event. The most common adverse event was neuropathy (in 55%); however, only 8% had grade 3 neuropathy and none had grade 4. Neuropathy improved or resolved in 68% of patients after the drug was discontinued.

This study shows that BV is highly active in relapsed or refractory HL; however, the PFS is short. Because no treatments are currently approved for relapsed or refractory HL progression after HDT/ASCR, these data may provide a basis for an investigational new drug application. However, more data are needed to determine if this drug can improve second- and even first-line therapy and thus impact outcomes.

### T-Cell Lymphoma

Patients with aggressive T-cell lymphoma generally have a poor outcome; however, systemic anaplastic T-cell lymphoma (sALCL) that expresses anaplastic kinase 1 (AKL1) is generally viewed as an exception. In a large retrospective cohort of patients with sALCL taken from sequential GELA studies, the most important prognostic factors were age older than 40 and beta-2 microglobulin. ALK1 expression was closely correlated with age and were not independent of each other in multivariate analysis. In patients younger than 40 years, ALK1 expression did not impact PFS or OS. However, younger patients with beta-2 microglobulin less than 3 had a poorer outcome. In patients older than 40 years, ALK1 expression was associated with a marginally superior PFS and OS.

Patients with relapsed or refractory sALCL were the subject of a phase II study of BV. In this study, Shustov et al. treated 58 patients with sALCL with the same regimen described previously for patients with HL. The OR and CR rates were 86% and 54%, respectively, with a median PFS of 41 weeks. Peripheral neuropathy was seen in 38% of patients (10% grade 3, no grade 4). OR and CR were similar for ALK1-positive and -negative patients, and hematologic toxicity was minimal. Given the poor outcome for older patients with sALCL, it would be very interesting to see if BV can safely and effectively be combined with CHOP; however, overlapping peripheral neuropathy may be a challenge.

Other forms of peripheral T-cell lymphoma (PTCL) remain a major clinical challenge. Pralatrexate was recently approved for treatment of relapsed or refractory disease, but additional agents and novel combinations are also necessary. Romidepsin is a histone deacetylase inhibitor with pleiotropic effects altering gene expression, activating apoptosis, and inhibiting angiogenesis. The final results of a multicenter phase II study of romidepsin confirmed early results from the NCI. In this study, the OR rate was 26%, with a CR/CRu rate of 13%. Median time to progression was 6 months and median duration of response was 12 months. Similar response rates were seen for PTCL not otherwise specified, angioimmunoblastic T-cell lymphoma, and sALCL (ALK1-negative). The most common treatment-related toxicities were nausea, vomiting, diarrhea, infection, asthenia, thrombocytopenia, and neutropenia. Cardiac toxicity was minimal (6%).

### Agents on the Horizon

Early-phase data emerged on several agents with early indications of clinical activity. For example, BTK is a tyrosine kinase downstream of the B-cell receptor. Inhibition of BTK induces apoptosis. In a phase I study of
PCI-32765, a BTK inhibitor, Fowler et al. evaluated the agent in patients with recurrent B-cell malignancies and found it to be well tolerated with minimal hematopoietic toxicity. The OR rates by intention-to-treat were 45% and 55% among evaluable patients. A phase I trial was also conducted in CLL, with similar manageable toxicity noted. Early indications are promising, with an OR rate of 64%. Interestingly, lymph nodes respond early, with a rise in peripheral clonal lymphocytosis, which then improves with further therapy. CAL-101 is a class I PI3K inhibitor selective for the δ-isofrom with expression restricted to hematopoietic cells. In knockout mice, lack of the δ-isofrom results in a B-cell defect. In vitro CAL-101 results showed enhanced apoptosis of B-cell lines. In a phase I study of CAL-101 in a heavily pre-treated population with CLL (median prior treatments, 5) including 36% of patients with del(17p), responses were seen at all dose levels. However, worsening lymphocytosis was common, with an OR rate of 26%. Adverse events included grade 3 or 4 neutropenia, thrombocytopenia, anemia, and transaminitis. In a study of the same agent in patients with indolent NHL and MCL, the toxicity profile was slightly different, with more grade 3 or 4 transaminitis and less neutropenia. The OR rate was 63% in patients with indolent NHL and 48% in those with MCL.

Preliminary data from a phase I combination of CAL-101 with rituximab or bendamustine in CLL and indolent NHL suggest that both agents can be safely combined with CAL-101. However, efficacy of the combination will only be evaluable in future phase II and III trials.

References


