Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology September 2008

Recent Advances in the Treatment of Non-Hodgkin Lymphoma

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A CME Activity
Approved for
1.0 *AMA PRA*
Category 1
Credit(s)™

Release date: September 2008
Expiration date: September 31, 2009
Estimated time to complete activity: 1 hour
Project ID #: 5470-ES-34

Abstract

Non-Hodgkin lymphomas (NHLs) comprise a large and diverse group of malignancies of lymphoid origin. NHL is the fifth most commonly diagnosed cancer in both males and females. NHLs are divided into indolent and aggressive phenotypes, and can be further categorized into multiple histopathologic subtypes. Optimal therapy is critically dependent on the identification of the correct NHL subtype, as the treatment for each differs. With the incorporation of rituximab into routine clinical use, the current approaches of therapy for indolent and aggressive NHLs include monoclonal antibody in combination with chemotherapy. Recently several novel agents and therapeutic regimens have been clinically evaluated for the treatment of various forms of NHL. Summarized here are the latest key clinical studies in the areas of indolent, aggressive, and T-cell lymphomas. Several of these studies were presented at recent international conferences, including the 10th International Conference on Malignant Lymphoma, held in Lugano, Switzerland this past June, and the 49th Annual Meeting and Exposition of the American Society of Hematology, held last December in Atlanta, Georgia. Familiarization with the updated results of these clinical trials will aid physicians in their recommendations for treatment and participation in clinical trials for their patients with NHL.

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Clinical Advances in HEMATOLOGY & ONCOLOGY™
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Expiration date: September 31, 2009
Estimated time to complete activity: 1 hour

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Statement of Need/Program Overview: Much has occurred and been presented at the various major hematology and oncology meetings over the past year regarding the emergence of new data impacting new standards of care for newly diagnosed multiple myeloma. These emerging data may not be fully understood by practicing hematologists/oncologists in the community setting. A one-year retrospective Clinical Roundtable Monograph is the ideal vehicle through which community-based physicians can learn about these recent advances.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the importance of existing and emerging agents in the natural history of NHL
- Review the results of clinical trials evaluating various treatments for NHL
- Identify future research directions for various therapies of NHL

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Classification Updates and Clinical Investigations In Indolent Non-Hodgkin Lymphoma

Bruce D. Cheson, MD

Non-Hodgkin lymphomas (NHLs) refer to a heterogeneous group of malignancies arising from the B cells, T cells, and natural killer (NK) cells. Successful therapy is dependent upon identifying the particular NHL subtype, as the treatment for each differs. Currently the World Health Organization (WHO) classification system is considered the global standard for the diagnosis and classification of NHL.[1,2] First published in 2001, the WHO system first divides NHL malignancies into B-cell or T-cell/NK-cell origin and then categorizes the subtype according to its precursor or mature morphology. Immunophenotyping and genetic pattern analysis further classify cell-specific malignancies. The process of revising and updating this system began in 2006, and the proposed revisions were recently reported on at the 10th International Conference on Malignant Lymphoma in Lugano, Switzerland.[3]

Several of these revisions are of particular relevance to the diagnosis of the indolent lymphomas. One controversial point of discussion was the continued use of the current grading system for follicular lymphoma (FL). FL is separated into three grades based on the number of centroblasts identified in neoplastic follicles in a defined microscopic field: <5 centroblasts, 5–15 centroblasts, and >15 centroblasts for grades 1, 2, and 3, respectively. Grade 3 FL can be further subdivided into 3A and 3B based on the absence or presence of solid sheets of centroblasts, respectively. Because FL grades 1 and 2 tend to show similar clinical behavior and outcome, they are often grouped together.[4] Grade 3A FL has been reported to have an indolent behavior, similar to grades 1 and 2, while grade 3B FL may have a more aggressive clinical phenotype.[5] This finding has prompted clinicians to recommend that the traditional grading system for FL be abandoned in favor of consolidating grades 1–3A into one group (indolent FL) and categorizing grade 3B as an aggressive form of FL. However, despite these discussions, the current grading system was retained in the updated revisions.[3] Instead it was decided that subsets of patients would be distinguished according to the particular variant of FL, including newly distinct variants, and whether the disease is highly localized This sentence doesn't make sense. A detailed description of the updated WHO classification is expected to be published in September 2008.

Several prognostic indices have been developed specifically for use in patients with FL. The Follicular Lymphoma International Prognostic Index (FLIPI) uses 5 independent risk factors to separate patients into 3 groups with distinct probabilities of survival.[6] The FLIPI calculates patient risk based on the following adverse prognostic factors: age >60 years, Ann Arbor stage III or IV disease, serum hemoglobin <12 g/dL, involvement of >4 lymph node groups, and elevated serum lactate dehydrogenase. Three risk groups are thus defined: low (0–1 factors), intermediate (2 factors), and high (≥3 factors). In the F2 study presented at the Lugano Conference, Federico and colleagues aimed to validate the FLIPI, and to identify novel indicators of prognostic value with the hope of creating a more accurate index.[7] The F2 investigators assessed a cohort of 942 FL patients receiving anti-lymphoma therapy; the median follow-up was 38 months and both overall survival (OS) and progression-free survival (PFS) were used as primary measurements of outcome. In addition to validating the prognostic utility of the FLIPI, the researchers performed a univariate analysis which identified 11 variables significantly impacting PFS. A multivariate analysis reduced this to five factors that are independently predictive of PFS: β2-microglobulin > the upper limit of normal (ULN), hemoglobin <12 g/dL, age older than 60 years, maximum diameter of the largest involved node >6 cm, and bone marrow involvement. These five factors were then verified in a prognostic model. Significantly, the F2 model identified patient risk groups that were highly correlated to 3-year PFS (low-risk: 92%, intermediate-risk: 70%, high-risk: 50%; $P<.00001$). Three-year OS rates were significantly correlated with this prognostic model as well (low-risk: 99%, intermediate-risk: 96%, high-risk: 84%; $P<.00001$). Importantly, this newer prognostic model was predictive in patients regardless of whether they had received rituximab therapy ($P<.0001$ for both positive and negative rituximab therapy). Thus, the F2 study not only validated the currently used FLIPI, but also further defined additional variables which may be of prognostic significance to identify patients at different risks of disease progression.

Two clinical trials investigating personalized vaccine therapy for FL were recently reported, each with discouraging results. At the ICML, Levy and colleagues presented the results of GTOP-99, a phase III clinical trial of patients with treatment-naive FL.[8] A total of 287 patients who had maintained at least a partial response (PR) over a rest period following 8 cycles of standard cyclophosphamide, vincristine, and prednisone (CVP) were randomized to receive either the individualized ID-KLH vaccine or a control immunotherapy. When patients who received the ID-KLH conjugate were analyzed for serum humoral immune

responses, those with a positive anti-ID immune response did experience an approximately two-fold improvement in PFS compared with those who were anti-ID negative (39.7 vs 18.1 months, respectively; *P*=.0017). However, no significant differences were observed in either PFS or the time to next anti-lymphoma therapy among the two treatment groups overall. In a second phase III clinical trial, the patient- and tumor-specific immunotherapy Specifid was compared with placebo in FL patients after rituximab therapy.[9] The primary trial endpoint, time to progression, failed to show a statistical superiority in the treatment arm compared with the control arm.

Bendamustine, a cytotoxic anticancer agent, is a bifunctional molecule with both alkylator and antimetabolite characteristics that is currently being evaluated for the treatment of NHL.[10,11] Multiple European studies have evaluated the activity of bendamustine in FL, both as a single agent and in combination therapy, with encouraging results.[12-14] The first interim results of a phase III trial from the German Study Group Indolent Lymphoma (StiL) was presented by Rummel and colleagues at the 2007 American Society of Hematology (ASH) annual meeting.[15] In this study, the combination of bendamustine (90 mg/m^2 d 1,2 every 4 weeks) plus rituximab (BR) was compared with standard cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (CHOP-R). In 273 evaluable patients, the overall response rate (ORR) was similar in both treatment groups (BR: 94%, CHOP-R: 93%), as was the complete response (CR) rate (BR: 51%, CHOP-R: 40%). However, the bendamustine-based regimen was associated with an improved safety profile over CHOP-R, with lower rates of hematologic toxicities, fewer infectious complications, and no alopecia. Bendamustine has also been evaluated in 3 US clinical trials. Two of these evaluated bendamustine monotherapy in the setting of rituximab-refractory patients with indolent NHL. In a phase II multicenter study, recently published by Friedberg and coauthors, single-agent bendamustine (120 mg/m^2) administered on the first two days of a 21-day cycle produced an ORR of 77% (CR or unconfirmed CR (CRu): 34%, PR: 43%).[16] Although several grade 3/4 hematologic toxicities were reported, these were reversible and considered an acceptable safety profile. A second single arm trial, presented by Kahl and colleagues at the 2007 ASH meeting, administered the same bendamustine monotherapy, again in rituximab-refractory patients.[17] The NHL histologies in this study included FL (53%), chronic lymphocytic leukemia/small lymphocytic lymphoma (26%), and marginal zone lymphoma (21%). In an analysis of the first 38 patients evaluated, the ORR was 84% after 6 bendamustine cycles, including 31% CR or CRu and 53% PR. The median PFS of these patients was 9.7 months. Importantly, these two trials show bendamustine to be significantly active in rituximab-refractory indolent NHL, and future clinical trials will continue to investigate the safety and efficacy of bendamustine in this setting. A phase II multicenter study recently published by Robinson and colleagues showed that the combination of bendamustine with rituximab was active in patients with relapsed indolent NHL or mantle cell lymphoma.[18] After a mean 5.2 cycles of therapy, the ORR was 92% (CR: 41%, CRu: 14%, PR: 38%) with a median PFS of 23 months (95% confidence interval: 20–26 months).

Table 1. Phase II Multicenter Study of Bendamustine in Rituximab-Refractory Indolent NHL: Response Rates

Patients	CR/ CRu, %	PR, %	SD, %	PD, %
FL (n=45)	37	44	4	11
SLL (n=11)	36	27	0	36
Lymphoplasmacytic (n=1)	100	0	0	0
MZL (n=2)	50	50	0	0
Transformed disease (n=15)	13	53	7	27
Total (n=74)	34	43	4	17

Adapted from Friedberg et al.[17]

*PR=CRu not confirmed by bone marrow evaluation.

CR=complete response; CRu=CR unconfirmed; FL=follicular lymphoma; MZL=marginal zone lymphoma; NHL=non-Hodgkin lymphoma; PD=progressive disease; PR=partial response; SD=stable disease; SLL=small lymphocytic leukemia.

Several other drugs are also under investigation for the treatment of indolent NHL. One of these is the proteasome inhibitor bortezomib.[19] Single-agent bortezomib displays activity in several of the indolent NHLs, its efficacy appears to be enhanced with the combination of rituximab.[20] A randomized phase II trial, which examined once versus twice weekly bortezomib combined with rituximab, showed both regimens to be active and well tolerated, with the weekly regimen associated with less toxicity than the twice-weekly regimen, with equal response rates.[21] Another phase II single-arm study is currently enrolling participants to evaluate the activity of bortezomib in combination with bendamustine and rituximab.[22] This trial is restricting recruitment to patients with relapsed or refractory FL who have received at least 4 prior doses of rituximab. Novel monoclonal antibodies directed against the CD20 receptor are also being evaluated. Preclinical results with one of these, GA101, were reported at the Lugano conference by Umana and colleagues.[23] In both a SCID mouse xenograft NHL model and cynomolgus monkeys, GA101 produced superior OS compared with rituximab. These promising results prompted Umana and colleagues to suggest that GA101 may become a "best-in-class" anti-CD20 therapy. Another anti-CD20 antibody, ofatumumab, recently showed dramatic results in a phase

I/II clinical trial.[24] In patients with relapsed or refractory FL, ofatumumab therapy resulted in immediate B-cell depletion and clinical response rates up to 63%. Veltuzumab, a second-generation anti-CD20 monoclonal antibody, was found to have antitumor effects in an in vivo cynomolgus monkey model, and to deplete circulating B cells in patients after a single infusion.[25] An objective response of 63% was observed in all NHL patients following veltuzumab therapy. Single-agent galiximab, a novel anti-CD80 monoclonal antibody, was previously shown to be safe and active in relapsed or refractory FL in a trial published by Czuczman and colleagues.[26] Galiximab was then tested as combination therapy with rituximab in a phase I/II study of patients with relapsed or refractory FL (not refractory to rituximab).[27] In this study, an ORR of 66% was observed, with a median PFS of 12.1 months. Based on these promising results, the CALGB 50402 trial was performed and presented at the Lugano conference.[28] This phase II study testing galiximab combined with rituximab in previously untreated patients showed an initial response rate of 69% (CR: 41%, PR: 28%). The ORR was 92% and the CR rate was 75% among patients with low FLIPI scores, and approximately 80% and 48%, respectively, for patients with intermediate scores, making this a potentially important regimen for such patients. A larger phase III trial has been initiated to compare this combination against rituximab alone.[29] The combination of rituximab plus epratuzumab, a humanized monoclonal antibody directed against CD22, is also under investigation as initial treatment for FL in a phase II study currently recruiting participants.[30]

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Clinical Investigations in Aggressive Non-Hodgkin Lymphoma

Jonathan Friedberg, MD

Among the proposed revisions to the WHO classification system the only major change relating to the aggressive subtypes of NHL was the suggested creation of a new category, termed intermediate between Burkitt lymphoma and diffuse large B cell lymphoma, to describe malignancies with characteristics of both Burkitt lymphoma and diffuse large B-cell lymphoma (DLBCL).[1] Although the histological diagnosis of these malignancies is generally easily distinguishable from Burkitt lymphoma, they often express immunological markers of Burkitt lymphoma, including c-myc, and have similar genetic lesions, most commonly the t(8;14) translocation.[2] The clinical prognosis is typically poor for these patients.

In light of the 50th anniversary of the discovery of Burkitt lymphoma, several studies presented at the Lugano conference focused on the treatment of this malignancy. One of these, from the National Cancer Institute, evaluated a less aggressive regimen comprised of dose-adjusted etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide (EPOCH) plus rituximab (EPOCH-R), along with intrathecal methotrexate.[3] Results were reported for 23 patients, including both HIV-positive and -negative individuals. Although this was a small study, the EPOCH-R regimen produced an excellent outcome, with every patient experiencing a CR or CRu. Only 1 relapse was reported.

Multiple clinical trials have also investigated emerging treatment options for DLBCL. One of these evaluated the utility of positron emission tomography (PET) as a response assessment tool to identify DLBCL patients who could be treated effectively with abbreviated chemotherapy and without involved-field radiation therapy (IFRT).[4] In this study DLBCL patients received a standard three cycles of CHOP-R, followed by PET scanning. Patients who were PET-positive went on to receive IFRT, the current standard therapy, while PET-negative patients were instead offered an additional cycle of CHOP-R. PET-negative patients (n=47) receiving the additional CHOP-R exhibited an excellent outcome, with only 1 relapse and a 97% 2-year OS rate. Of the 16 PET-positive patients who received IFRT, 3 relapses and 2 lymphoma-related deaths were reported. Importantly, of the 65 enrolled patients, 75% were PET-negative after the initial three CHOP-R cycles. According to the study authors, Sehn and colleagues, PET scanning mid-therapy can identify a large proportion of patients who can be spared the increased toxicity associated with IFRT while maintaining a satisfactory clinical outcome. This approach is clearly worthy of further study.

A dose-dense rituximab regimen was investigated in a German study of elderly DLBCL patients.[5] Previously these investigators had shown that when CHOP and rituximab are administered concomitantly rituximab trough levels do not achieve a plateau until the fifth treatment cycle.[6] Therefore, Pfreundschuh and colleagues evaluated the safety and activity of a dose-dense regimen consisting of 6 cycles of biweekly CHOP (CHOP-14) combined with 12 doses of rituximab (on days 0, 1, 4, 8, 15, 22, 29, 43, 57, 71, 85, and 99), with the goal of achieving high rituximab trough levels earlier in the course of therapy. Because of 3 therapy-associated deaths among the first 20 patients treated, subsequent patients received mandatory prophylactic therapy with levofloxacin, acyclovir, and co-trimoxazole. In 97 evaluable elderly patients, rituximab plateau trough levels were achieved by day 1 and maintained throughout therapy. When these elderly patients were compared with individuals from a previous trial who had received CHOP-14 with only 8 cycles of rituximab, they exhibited a higher rate of CR (83% vs 78%), although event-free survival (EFS) and OS were similar among the cohorts. Interestingly, a subgroup analysis found that patients with a poor FLIPI risk did show superior CR rates (81% vs 68%) and increased 1-year EFS (74% vs 65%). The German group plans to prospectively compare this dose dense rituximab regimen to the standard R-CHOP 14 regimen.

A third DLBCL study, performed by Hamlin and colleagues, investigated consolidation therapy with 90Y ibritumomab tiuxetan radioimmunotherapy (RIT) in elderly patients (>60 years) with intermediate high– and high-risk disease.[7] Yttrium 90Y ibritumomab tiuxetan is a radioimmunotherapeutic agent comprised of ibritumomab, a murine monoclonal anti-CD20 antibody, linked by the chelator tiuxetan to the radioisotope 90Y. The anti-CD20 antibody portion causes targeted delivery of the agent to CD20-positive DLBCL cells, allowing the isotope to deliver specific and direct radiation, thereby minimizing systemic radiation toxicity.[8,9] In this study 60 elderly DLBCL patients (median age 75 years) who were ineligible for stem cell transplantation received standard CHOP-R induction therapy for six cycles, followed 6–9 weeks later by consolidation therapy with RIT in patients with at least stable disease. In the intent-to-treat group (58 evaluable patients), the rates of OS and PFS were 67% and 59%, respectively, at a median follow-up of 15 months. At a median 23-month follow-up in 38 patients who went on to receive RIT consolidation, the OS and PFS rates were 88% and 80%, respectively. The median PFS was not reached in patients receiving RIT, but

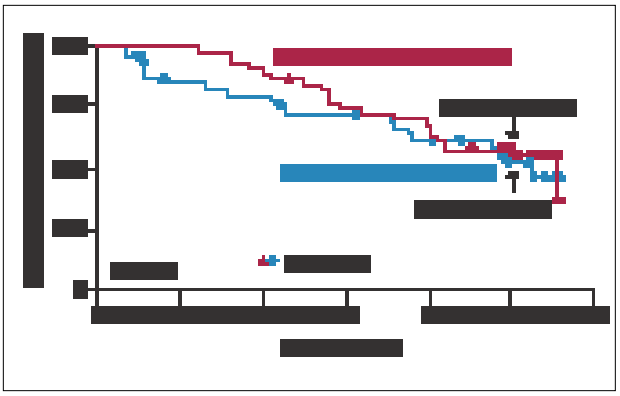

Figure 1. OSHO 39: R-MCP vs MCP in advanced MCL overall survival (OS).

MCL=mantle cell lymphoma; MCP=mitoxantrone, chlorambucil, prednisolone; R-MCP=MCP + rituximab

was 3.6 months for those not receiving RIT. Importantly, 11 patients continued to experience improved responses after RIT, including 7 patients who improved from CRu to CR, and 4 patients who improved from PR to either CR or CRu. A similar approach of radioimmunotherapy consolidation with iodine-131 tositumomab following R-CHOP therapy for diffuse large B cell lymphoma is currently under investigation by the Southwest Oncology Group.

Finally, a novel oral Syk kinase inhibitor, fostamatinib disodium, was evaluated in a phase I/II clinical study of patients with relapsed or refractory DLBCL and other forms of NHL.[10] Syk, a protein kinase that transmits survival signals from the B-cell receptor, has emerged as a promising target in DLBCL.[11] Furthermore, in vitro studies have found that pharmacological inhibition of Syk induces cell death in DLBCL cell lines.[12] In the phase I portion of this study, the dose-limiting toxicity was neutropenia, and a 200 mg twice daily dose was chosen for phase II studies. Sixty-eight patients were enrolled for the phase II portion, 23 of whom had DLBCL (12 after ASCT) and were evaluable after 57 days of therapy. Of these, 5 patients exhibited a PR, and one additional patient had ongoing stable disease. Because these patients had heavily pretreated disease, the results were considered encouraging, and future trials are planned to further test fostamatinib disodium in DLBCL, with plans to target a specific subset of disease that may be more responsive.

Two abstracts focused on investigational therapies in MCL, both of which called into question the benefit of rituximab in this NHL subgroup. The first, presented by Zelenetz and colleagues, was a retrospective analysis of the treatment of MCL patients at the Memorial Sloan-Kettering Cancer Center in New York.[13] In this analysis, 79 patients were treated with four cycles of induction therapy with CHOP-14, either with (n=59) or without (n=20) rituximab. This was followed by standard consolidation therapy and transplant conditioning, with subsequent rituximab as post-transplant maintenance therapy. Importantly, there was no difference in clinical outcome between patients who did or did not receive rituximab, either as induction therapy or maintenance therapy. A second study, conducted by Herold and colleagues, compared the standard chemotherapy regimen of mitoxantrone, chlorambucil, and prednisolone (MCP), with MCP plus rituximab (MCP-R) in patients (N=90) with MCL.[14] No significant differences were noted in several clinical outcomes, including median PFS (18.5 vs 20 months), median EFS (13 vs 18 months), and median OS (52 vs 56 months) (Figure 1). Together, both of these trials emphasize the increased need for novel agents and improved treatment regimens for this poor-prognosis, aggressive form of NHL.

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Clinical Investigations in T-cell and NK-cell Non-Hodgkin Lymphoma

Steven Rosen, MD

As with the subgroups of NHL discussed above, proposed revisions to the WHO classification of malignancies of T-cell and NK T-cell origin were also presented at the Lugano conference.[1] The major change for this subgroup was a new distinction between anaplastic lymphoma kinase (ALK)-positive and -negative forms of anaplastic large cell lymphoma (ALCL). ALK is an oncogene that results in increased transformation potential.[2,3]

In Western countries, up to 15% of all lymphomas are of T-cell origin.[4,5] A large international study retrospectively evaluated the proportion of T-cell lymphoma subtypes from 22 sites in North America, Europe, and Asia.[6] A majority (87.8%) were identified as either peripheral T-cell lymphoma (PTCL) or NK T-cell lymphoma (NKTCL). When considering the specific subtypes, PTCL not otherwise specified (NOS) was most common (25.9%), followed by the angioimmunoblastic T-cell lymphoma (AILT) subtype (18.5%). Approximately 10.4% of the cases were identified as NKTCL, and 9.6% were adult T-cell leukemia/lymphoma (ATLL). ALK-positive and ALK-negative ALCL comprised 6.6% and 5.5% of cases, respectively, and 4.7% were enteropathy-type PTCL. The 5-year failure-free survival rates for each of the T-cell lymphomas were as follows: PTCL NOS (20%); ATCL (18%); NKTCL (29%, except 6% for extranodal NKTCL); ALK-positive ATLL (60%); ALK-negative ATLL (36%); and enteropathy-type PTCL (4%).

Few studies have validated the international prognostic index (IPI) in patients with PTCL, mainly due to its rarity and geographic distribution. Therefore, Watanabe and colleagues undertook a review of 1,084 histological specimens from six multicenter clinical studies in which hematopathologists made consensus diagnoses according to WHO classifications.[7] In this study, 136 cases were identified as PTCL, subdivided as PTCL-NOS (n=53), AILT (n=46), ALCL (n=18), extranodal NKTCL (n=17), and NKTCL (n=2). In univariate analysis, four variables were identified as poor prognostic factors for OS: low total serum protein (<6.3 g/dL), involvement of the gastrointestinal tract, pathological subtype (PTCL-NOS and NKTCL vs AILT and ALCL), and low serum albumin (<3.7 g/dL). However, in a multivariate analysis, only low total serum protein (P=.004) and PTCL-NOS/NKTCL subtypes (P=.024) were found to be independent risk factors. Together this allowed for the development of a new prognostic model for PTCL, which could effectively distinguish three patient risk groups (P<.0001). Patients in the low-, intermediate-, and high-risk groups experienced 5-year OS rates of 61.2%, 42.3%, and 12.5%, respectively.

In another attempt to better determine prognostic indicators in these NHL subgroups, Schmitz and colleagues performed a retrospective analysis of several German clinical trials.[8] Among the total group of 331 patients, the 3-year OS and EFS rates were 65% and 51%, respectively; however, when patients were subdivided according to the IPI, significant differences in their respective OS rates were noted. In a multivariate analysis, the only IPI factor that did not significantly impact OS was advanced tumor stage. Patients less than 60 years of age experienced superior 3-year EFS rates compared to elderly patients (71% vs 50%) when administered etoposide combined with either CHOP-14 or CHOP-21. From these results, the authors determined that the IPI was in fact of robust value for prediction of OS and EFS in patients with T-cell NHL.

A report by Nickelsen and colleagues evaluated autologous stem cell transplantation (ASCT) in 298 patients with mature T-cell lymphomas.[9] At the time of ASCT, 34.1% of patients had achieved a CR, 55.6% were chemosensitive, and 10.4% were either refractory to chemotherapy or untested. At a median follow-up of 39 months, 44.3% of the patients had relapsed within a median period of 4 months; only 31.8% of these patients were alive at the time of analysis. At 2 years the rate of non-relapse mortality was 9.5% and the relapse rate was 43.6% (Figure 2). This translated to a PFS rate of 46% and an OS rate of 60%. Refractory disease at the time of ASCT was the only significantly poor prognostic variable in multivariate analysis (P=.002). Additionally, the rate of relapse was significantly higher in refractory patients (P=.005). Taken together, the authors concluded that patients with chemorefractory T-cell lymphoma gained no benefit from high-dose therapy followed by ASCT. Although a total of 84% of patients had chemosensitive disease, approximately half experienced a relapse of disease.

Several abstracts at the Lugano conference reported results of novel agents in the treatment of T-cell and NK-cell NHL. One of these reported the effect of everolimus, a specific inhibitor of the mammalian target of rapamycin (mTOR).[10] In this phase II trial patients received 2, 6, or 12 cycles of everolimus (10 mg daily, 28-day cycle); patients were restaged after each timepoint.[11] Of 25 enrolled patients,

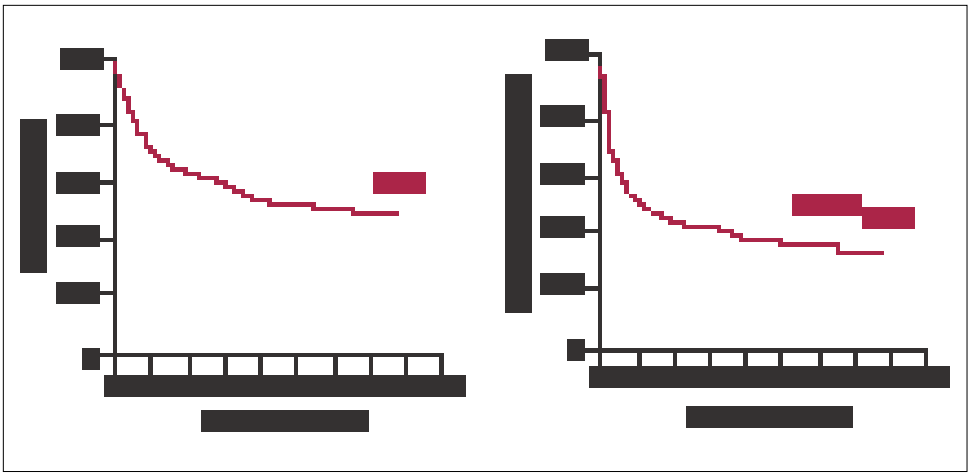

Figure 2. Autologous stem cell transplantation (SCT) in peripheral T-cell lymphoma: overall survival and progression-free survival (PFS). Multivariate Cox analysis: Refractory disease was the only significant factor for PFS. (Trend for high/high-intermediate IPI at diagnosis)

Data from Nickelsen et al, on behalf of the Lymphoma WP of the European Group for Blood and Marrow Transplantation (unpublished results).

8 individuals were diagnosed with T-cell lymphomas. In these patients, the ORR was 63%. A separate trial, by Jaccard and colleagues, described the effect of L-asparaginase in the treatment of extranodal NKTCL.[12] L-Asparaginase displayed activity in 24 out of 27 patients; a CR was documented in 12 patients. At the time of the report, 13 patients were still alive (median follow-up 14 months) with 9 patients experiencing a persistent CR. Future studies will further test the efficacy of L-asparaginase in this subgroup of patients. Two studies evaluated a novel antibody, KW-0761, directed against the chemokine receptor CCR4.[13,14] Both studies showed promising results and future investigation in T-cell lymphomas is warranted.

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Recent Advances in the Treatment of Non-Hodgkin Lymphoma

CME Post-Test: *Circle the correct answer for each question below.*

1. Which of the following factors were NOT identified as independently predictive of PFS in a multivariate analysis of the F2 study, discussed by Dr. Cheson?

   a. b2-microglobulin greater than the upper limit of normal
   b. age >60 years
   c. >6 cm maximum diameter of the largest positive node
   d. negative bone marrow involvement

2. Which of the following is NOT a characteristic of bendamustine?

   a. It is an alkylator
   b. It is an antimetabolite
   c. It is a purine analog
   d. It is a pyrimidine analog

3. The first interim results from a phase III study by the German StiL group, discussed by Dr. Cheson, revealed that the bendamustine-rituximab combination produced _____ rates of OS compared with CHOP-R in patients with indolent NHL.

   a. similar
   b. superior
   c. reduced
   d. slightly higher

4. Ofatumumab, a novel antibody directed against _____, recently produced clinical response rates up to 63% in a phase I/II clinical trial.

   a. CD80
   b. CCR4
   c. CD20
   d. Bcl-2

5. In a study discussed by Dr. Friedberg, _____ of patients were PET-negative after an initial 3 cycles of CHOP-R.

   a. 47%
   b. 75%
   c. 83%
   d. 92%

6. A DLBCL study discussed by Dr. Friedberg showed that consolidation therapy with 90Y ibritumomab tiuxetan produced a _____ OS rate at a median follow-up of 23 months.

   a. 59%
   b. 67%
   c. 88%
   d. 90%

7. Proposed revisions to the WHO classification of T-cell and NK T-cell lymphomas, discussed by Dr. Rosen, included the recognition of both _____ -positive and -negative forms of ALCL.

   a. Bcl-2
   b. CD20
   c. CD80
   d. ALK

8. In a summary of T-cell lymphomas presented by Vose and discussed by Dr. Rosen, the 5-year failure-free survival rate associated with PTCL NOS was _____.

   a. 20%
   b. 29%
   c. 36%
   d. 60%

9. In a study of ASCT discussed by Dr. Rosen, the relapse rate at 2 years following ASCT was _____.

   a. 34.1%
   b. 43.6%
   c. 55.6%
   d. 84%

10. The mTOR inhibitor everolimus produced an ORR of _____ in patients with T-cell lymphomas.

    a. 8%
    b. 25%
    c. 27%
    d. 63%

Evaluation Form: Recent Advances in the Treatment of Non-Hodgkin Lymphoma

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the importance of existing and emerging agents in the natural history of NHL	1	2	3	4	5
2. Review the results of clinical trials evaluating various treatments for NHL	1	2	3	4	5
3. Identify future research directions for various therapies in NHL	1	2	3	4	5

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice	1	2	3	4	5
Enhanced my current knowledge base	1	2	3	4	5
Addressed my most pressing questions	1	2	3	4	5
Provided new ideas or information I expect to use	1	2	3	4	5
Addressed competencies identified by my specialty	1	2	3	4	5
Avoided commercial bias or influence	1	2	3	4	5

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