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Another Summer of Hematology

Highlights in Leukemia, Lymphoma, and Multiple Myeloma
From the 15th Congress of the European Hematology Association and the 2010 American Society of Clinical Oncology Annual Meeting

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Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologists, nurses, and other health care professionals involved in the management of patients with leukemia, lymphoma, and myeloma.

Statement of Need/Program Overview: The treatment of patients with leukemia, lymphoma, and myeloma has improved response rates and survival outcomes dramatically. Several novel and emerging agents are being investigated in hematologic malignancies, including histone deacetylase inhibitors, nucleoside analogues, monoclonal antibodies, immunotherapies, and novel targeted therapies. It is critical that clinicians treating patients with hematologic malignancies have the latest information from major meetings. The American Society of Clinical Oncology (ASCO) and the European Hematology Association (EHA) annual meetings are among the premier outlets for the release of new clinical data. With the multitude of presentations made at these meetings, there is a need for supplementary materials that distill information, cull the most important breakthrough findings, and summarize data for subsequent integration into clinical care.

Educational Objectives

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

- Describe the importance of new study findings and clinical trial data in the natural history of patients with leukemia, lymphoma, and myeloma
- Explain the results of these new study findings, including current clinical trials evaluating therapy in the treatment of leukemia, lymphoma, and myeloma
- Describe how to integrate into clinical practice the latest knowledge on emerging therapies and methods for treating patients with leukemia, lymphoma, and myeloma in an effort to improve current prognosis
- Identify future research directions for all therapies in leukemia, lymphoma, and myeloma

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Another Summer of Hematology

Highlights in Leukemia, Lymphoma, and Multiple Myeloma From the 15th Congress of the European Hematology Association and the 2010 American Society of Clinical Oncology Annual Meeting

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The sun shone brightly over the waters of Lake Michigan and the Mediterranean Sea as the almost simultaneous meetings of the American Society of Clinical Oncology (ASCO) and the European Hematology Association (EHA) took place this summer. Clinicians and scientists from around the globe convened in Chicago and Barcelona to review and discuss emerging data on novel and existing therapies for the myriad hematologic disease states.

Chronic Myelogenous Leukemia

Imatinib, an inhibitor of B-cell receptor (BCR)-ABL kinase, has been considered the standard of care for patients with chronic myelogenous leukemia (CML) since it emerged as one of the first oncology therapeutics to attack a specific cellular target. However, recent data indicate that dasatinib, a second-generation BCR-ABL kinase inhibitor, may provide a more effective alternative for this patient population.[1] Dr. Hagop Kantarjian presented the results of a randomized, phase III trial designed to compare dasatinib with standard imatinib as first-line therapy for chronic-phase CML.[2] These data were also presented at the Presidential Symposium of the EHA meeting by Dr. Michele Baccarani.[3] Five hundred and nineteen patients with treatment-naïve Philadelphia (Ph)-positive CML-chronic phase stratified by Hasford scores were randomized to receive either dasatinib 100 mg once daily (n=259) or imatinib 400 mg once daily (n=260). The primary endpoint was confirmed complete cytogenetic response (CCyR) by 12 months detected in 2 consecutive assessments. Secondary endpoints were lack of Ph-positive metaphases in bone marrow, major molecular response (MMR), times to CCyR and MMR, and progression-free survival (PFS) and overall survival (OS). The median time to achieve MMR was faster in the dasatinib arm than in the imatinib arm (6.3 vs 9.2 months), and, overall, dasatinib induced higher MMR rates than did imatinib across all Hasford risk groups (low risk, 56% vs 36%; intermediate risk, 45% vs 28%; and high risk, 31% vs 16%; Table 1). The rate of progression to accelerated-phase/blast-crisis CML was higher with imatinib than dasatinib (3.5% vs 1.9%), but no patient who achieved MMR progressed to accelerated phase or blast crisis, and only 2 patients who achieved CCyR progressed to accelerated phase or blast crisis (1 in each arm). The 12-month OS was similar for both arms; 97.2% versus 98.8% for dasatinib and imatinib, respectively. The likelihood of achieving CCyR at any time with dasatinib was approximately twice that with imatinib; the hazard ratio (HR) was 1.53 (P<.0001). In addition, the

Table 1. Response to Once Daily Dasatinib (100 mg) and Imatinib (400 mg) in Treatment-Naïve Patients With Chronic Phase Chronic Myelogenous Leukemia

Outcome, %	Dasatinib (n=259)	Imatinib (n=260)	*P* Value
CCyR			
3 months	54	31	
6 months	73	59	
9 months	78	67	
12 months	83	72	.0011
12-month confirmed CCyR	77	66	.0067
MMR			
3 months	8	0.4	
6 months	27	8	
9 months	39	18	
12 months	46	28	<.0001

CCyR=complete cytogenetic response; MMR=major molecular response.

Data from Baccarani M et al.[3]

likelihood of achieving MMR at any time with dasatinib was significantly higher than with imatinib; 52% versus 34% ($P<.00003$), HR, 2.01 ($P<.0001$). Overall, both treatments were well tolerated with a similar frequency of adverse events (AEs) and a similar proportion of patients in each treatment arm remaining on therapy: 84.5% for dasatinib and 81.4% for imatinib. However, more patients in the imatinib arm required dose escalation (14% vs 5%). Since 12-month CCyR and MMR have been shown to have a strong predictive outcome for long-term PFS in patients with CML, the results of this study indicate that dasatinib as initial therapy may lead to improved long-term clinical benefit in this population.

Hodgkin Lymphoma

The debate regarding optimal treatment for early-stage, favorable-prognosis Hodgkin lymphoma (HL) is unresolved. Treatment options include various chemotherapy regimens and combined modality treatment with chemotherapy and radiation therapy. Dr. Andreas Engert reported the final analysis of the randomized HD10 trial from the German Hodgkin Study Group at the EHA meeting.[4] This study was designed to address the number of chemotherapy cycles and the radiation dose needed to achieve optimal outcome in 1,370 patients with early-stage disease receiving ABVD (doxorubicin [Adriamycin] 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2) and involved field radiation therapy (IFRT). The study arms were balanced for age, sex, disease stage and histology, performance status, and risk factors prior to randomization to 1 of 4 treatments: 4 cycles of ABVD with 30 Gy, 4 cycles of ABVD with 20 Gy, 2 cycles of ABVD with 30 Gy, and 2 cycles of ABVD with 20 Gy. At the reported median follow-up of 79–81 months, there was no significant difference in terms of OS at 5 years (97.1% vs 96.6%), freedom from treatment failure (97.6% vs 97.5%), or PFS (93.5% vs 91.2%) for 4 and 2 cycles of chemotherapy, respectively. An analysis of the impact of IFRT showed no significant difference between patients receiving 30 Gy and those receiving 20 Gy in terms of OS (97.6% vs 97.5%), freedom from treatment failure (93.4% vs 92.9%), and PFS (93.7% vs 93.2%). Analysis of all 4 treatment groups failed to show an advantage between 2 and 4 cycles of ABVD, irrespective of the dose of radiation received. However, significant differences were determined for the AEs reported in each treatment arm. Not surprisingly, the overall number of AEs was greater for 4 cycles of ABVD than for 2 cycles (52% vs 33%), including alopecia (28% vs 15%) and leukopenia (24% vs 15%). There was also a difference in AEs between the IFRT groups. The total number of AEs was greater with 30 Gy (8.7% vs 2.9%), and higher doses were associated with more frequent individual events, including dysphagia (3% vs 2%) and mucositis (3.4% vs 0.7%). Based on these observations, the German Hodgkin Study Group now considers 2 cycles of ABVD followed by 20 Gy IFRT as the new standard of care for early-stage HL patients with favorable prognosis.

At ASCO, Dr. Gallamini, for the Gruppo Italiano Terapie Innovative nei Linfomi (GITIL), presented a retrospective study designed to evaluate whether early chemotherapy intensification with BEACOPP (bleomycin, etoposide, doxorubicin [Adriamycin], cyclophosphamide, vincristine, procarbazine, and prednisone) can improve the outcome of high-risk, advanced-stage HL patients treated with ABVD.[5] The GITIL demonstrated previously that early interim 2-[18F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) performed after 2 courses of ABVD (PET2) is highly predictive of treatment response and PFS in HL patients.[6] The current study was designed to evaluate whether early dose intensification with BEACOPP in PET2–positive HL patients with advanced-stage disease leads to an improved outcome. Among the 164 patients enrolled in this study at 9 different centers, 27 (17%) were PET2 positive and received escalated/standard BEACOPP (4 cycles of each). The remaining 135 patients (83%) were PET2 negative and remained on ABVD. Other prognostic factors (eg, age, International Prognostic Index [IPI] score >3, and bulky disease), were well balanced between the 2 groups ($P=.94$, $P=.49$, and $P=.48$, respectively). PET2 scans were reviewed centrally via a 5-point semi-quantitative score, with liver as the reference organ for FDG uptake.[7] Dr. Gallamini reported a good concordance rate among centers using this approach. The treatment outcome with BEACOPP chemotherapy intensification in PET2–positive patients was comparable to that typically seen with this regimen in all patients. After a follow-up of up to 48 months, the failure-free survival for the 152 patients correctly treated according to the centralized PET review was 91.3% for all patients and 96.2% and 60.5% for PET2–positive and PET2–negative patients, respectively (Figure 1). Dr. Gallamini noted that the clear advantage to this approach is that the toxic effects of the aggressive BEACOPP regimen are avoided in patients who are unlikely to benefit from this therapy (approximately 80% of the population in this study). This therapeutic strategy is now being assessed prospectively in several multicenter clinical trials in the United States and Europe.

At ASCO, Dr. Anna Sureda reported interim data from a phase II evaluation of panobinostat (LBH589) in patients with relapsed/refractory HL following autologous stem cell transplant.[8] Panobinostat is an oral histone deacetylase inhibitor with durable antitumor activity as monotherapy in heavily pretreated patients with relapsed/

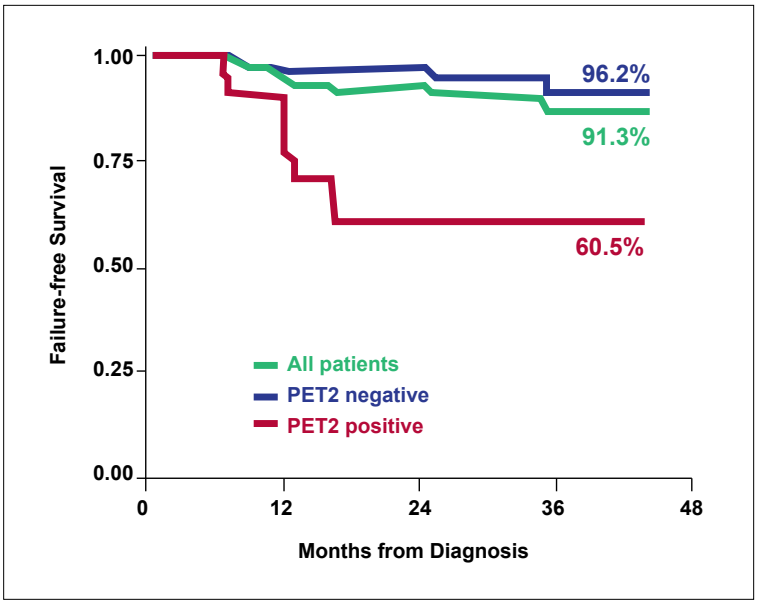

Figure 1. Failure-free survival curves in patients with Hodgkin lymphoma (n=152) treated with ABVD (PET2 negative) or escalated/standard BEACOPP (PET2 positive). ABVD=doxorubicin [Adriamycin] 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2. Standard BEACOPP=bleomycin, etoposide, doxorubicin [Adriamycin], cyclophosphamide, vincristine, procarbazine and prednisone (21-day cycles followed by a therapy-free period on days 16–21). Escalated BEACOPP=bleomycin, etoposide, doxorubicin [Adriamycin], cyclophosphamide, vincristine, procarbazine and prednisone (14-day cycles).

Data from Gallamini A et al.[6]

refractory HL.[9] The current study was designed to determine the efficacy of this agent in such patients following high-dose chemotherapy. The 129 patients, all ages 18 or older, were enrolled into a 2-stage Simon optimal design study (stage 1: n=35; stage 2: n=67). All patients had confirmed classical HL with disease progression following high-dose chemotherapy plus autologous stem cell transplant. Panobinostat was administered at 40 mg 3 times per week in 21-day cycles, with dose interruptions or modifications as needed. Response was assessed by computed tomography/magnetic resonance imaging every 2 cycles, and the primary endpoint was overall response rate (ORR). Secondary endpoints were time to and duration of response, PFS, OS, and safety and tolerability. An ORR of 26% was reported, and disease control—expressed as complete response (CR), partial response (PR), and stable disease (SD)—was achieved by 111 enrolled patients (86%) in the study. The median time to response was 7 weeks (range, 4–51 weeks), and the median duration of response was more than 7.2 months. PFS was more than 5.9 months. Among the patients who experienced a response (CR/PR, n=33), 50% had been resistant to their last therapy, and 54% showed a response after 2 cycles. Of the total population, 45% discontinued therapy with panobinostat due to disease progression (30%) or AEs (9%). Reversible thrombocytopenia (grade 3/4) was the most common treatment-related AE (77.5% of all patients). Diarrhea, nausea, fatigue, anemia, and vomiting were also commonly reported (mostly grade 2). Dr. Sureda concluded that panobinostat appears to offer a safe and effective therapeutic option for this HL population and warrants further evaluation.

Non-Hodgkin Lymphoma

Follicular Lymphoma

Dr. Ruth Pettengell, on behalf of the European Group for Blood and Marrow Transplantation Lymphoma Working party, presented data at ASCO from a randomized study designed to determine the effects of in vivo purging with rituximab and subsequent rituximab maintenance on PFS in patients with relapsed or resistant follicular non-Hodgkin lymphoma (NHL) undergoing high-dose therapy and stem cell support with BEAM (BCNU [carmustine], etoposide, cytosine arabinoside, melphalan) conditioning.[10] Of the planned 420 patients, 280 entered the study. Among the 279 patients who were evaluable for response, 16 were in first remission, 222 were in second remission, and 41 were in third remission. Eighty-three had achieved CR, and 196 had a very good PR to prior induction chemotherapy, with limited bone marrow infiltration (<25% B lymphocytes). Patients were randomized to receive in vivo rituximab purging and rituximab maintenance or observation, or rituximab maintenance or observation alone without rituximab purging according to a 2 × 2 design (Figure 2). The primary endpoints of the study were PFS and response rates; safety and OS were secondary endpoints. The rate of 5-year PFS was 54.1% for patients receiving in vivo purging versus 48% for no purging, and 59.4% for patients receiving rituximab maintenance versus 42.0% for no maintenance (Figure 3). When compared to patients who received neither rituximab purging nor rituximab maintenance, patients who received both showed a significant improvement in PFS (5% vs 37.6%),

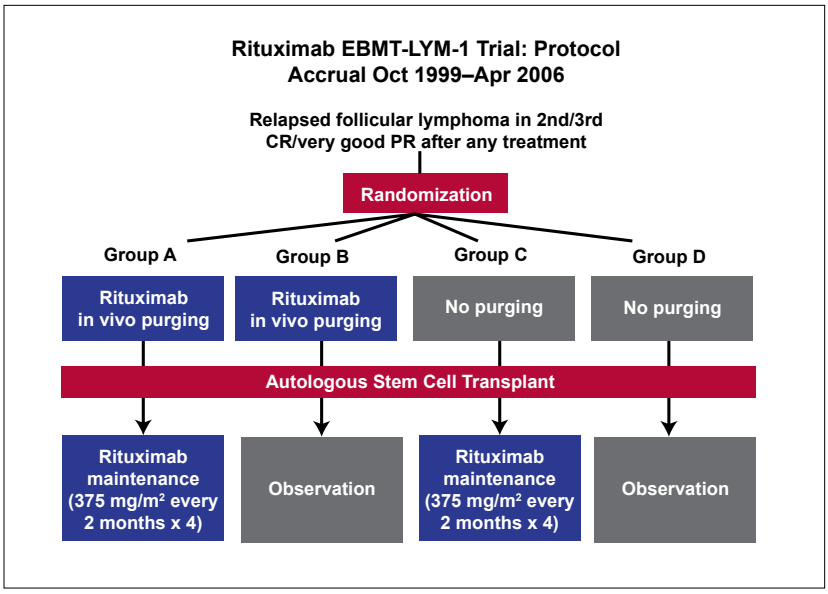

Figure 2. The effect of rituximab maintenance on progression-free survival in patients with refractory or resistant follicular non-Hodgkin lymphoma undergoing high-dose therapy with BEAM (carmustine, cytarabine, etoposide, and melphalan) conditioning: study schema.

Data from Pettengell R et al.[10]

and the OS at 5 years was 80% (95% confidence interval [CI], 75.5–85.0%; Figure 4). Dr. Pettengell noted that engraftment and hematopoietic recovery are not compromised with rituximab purging, and no AE was seen on peripheral blood progenitor cell harvesting. There were also no unexpected AEs reported, leading to the conclusion that salvage therapy post-autograft combined with rituximab maintenance is safe and effective in patients with relapsed or resistant follicular NHL.

Emerging Agents in NHL

Several reports were made at these meetings of intriguing therapeutic approaches that hold promise for the future treatment of NHL patients. Dr. Nathan Fowler and colleagues presented initial data in Chicago from a phase I trial of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 in patients with relapsed NHL.[11] PCI-32765 is an orally bioavailable small molecule that binds irreversibly with a specific cysteine molecule of Btk expressed in tumor cells. Such binding blocks B-cell receptor signaling, inducing apoptosis. The objectives of the study presented were to establish the safety, pharmacokinetics, and maximum tolerated dose (MTD) of PCI-32765. In αddition, pharmacodynamic activity was measured by drug occupancy of Btk, and a preliminary assessment of efficacy was made by measuring tumor volume. Dr. Fowler reported on the first 40 of 47 patients enrolled in this ongoing study. Therapy was well tolerated, with minimal toxicities at doses up to 12.5 mg/kg/day, and an MTD had yet to be reached. A preliminary assessment of tumor response is encouraging, especially when examined by histology (Table 2).

Dr. Gilles Salles presented a paper at EHA reporting data from a phase II study in patients with relapsed/refractory indolent NHL treated with GA101.[12] GA101 is a fully humanized, third-generation, glycoengineered anti-CD20 immunoglobulin G1 monoclonal antibody. It binds with high affinity to the CD20 type II epitope, resulting in the induction of antibody-dependent cytotoxicity 5- to 100-fold greater than that seen with classic anti-CD20 antibodies such as rituximab.[13] In a phase I/II clinical trial in patients with relapsed/refractory CD20-positive lymphoid malignancies, GA101 had a similar safety profile to rituximab, and promising efficacy was observed. Forty patients were randomized to 1 of 2 dose cohorts: a low dose of 400 mg for all infusions (LD, n=18) or a high dose of 1,600 mg on days 1 and 8 and 800 mg thereafter (HD, n=22). The therapy was given on days 1, 8, 21, and 21 for a total of 9 infusions over a 6-month period. The primary endpoint of the study was response rate, with secondary endpoints of safety and pharmacokinetics. The patients were all heavily pretreated (the median number of prior therapies was 4), and the 2 groups matched well for follicular histology (LD: n=14, HD: n=20) and median age (LD: 51 years [range, 42–79], HD: 61.5 years (range, 44–76). The majority of patients had received prior rituximab therapy (30 of 40), to which many had showed resistance (LD: 12 of 18, HD: 11 of 22). GA101 was well tolerated in both cohorts, the most frequently observed toxicities being grade 1/2 infusion-related reactions (LD: 72% of patients, HD: 73% of patients). Serious AEs were reported for 11 patients, 5 of which were deemed related to GA101 (LD: n=1, HD: n=4). During treatment, related grade 3/4 AEs were mostly hematologic in nature and included transient neutropenia (n=3 in HD) and thrombocytopenia (n=1 in HD); 4 patients experienced at least 1 grade 3/4 infection. At the end of the study, 95% of patients were evaluable

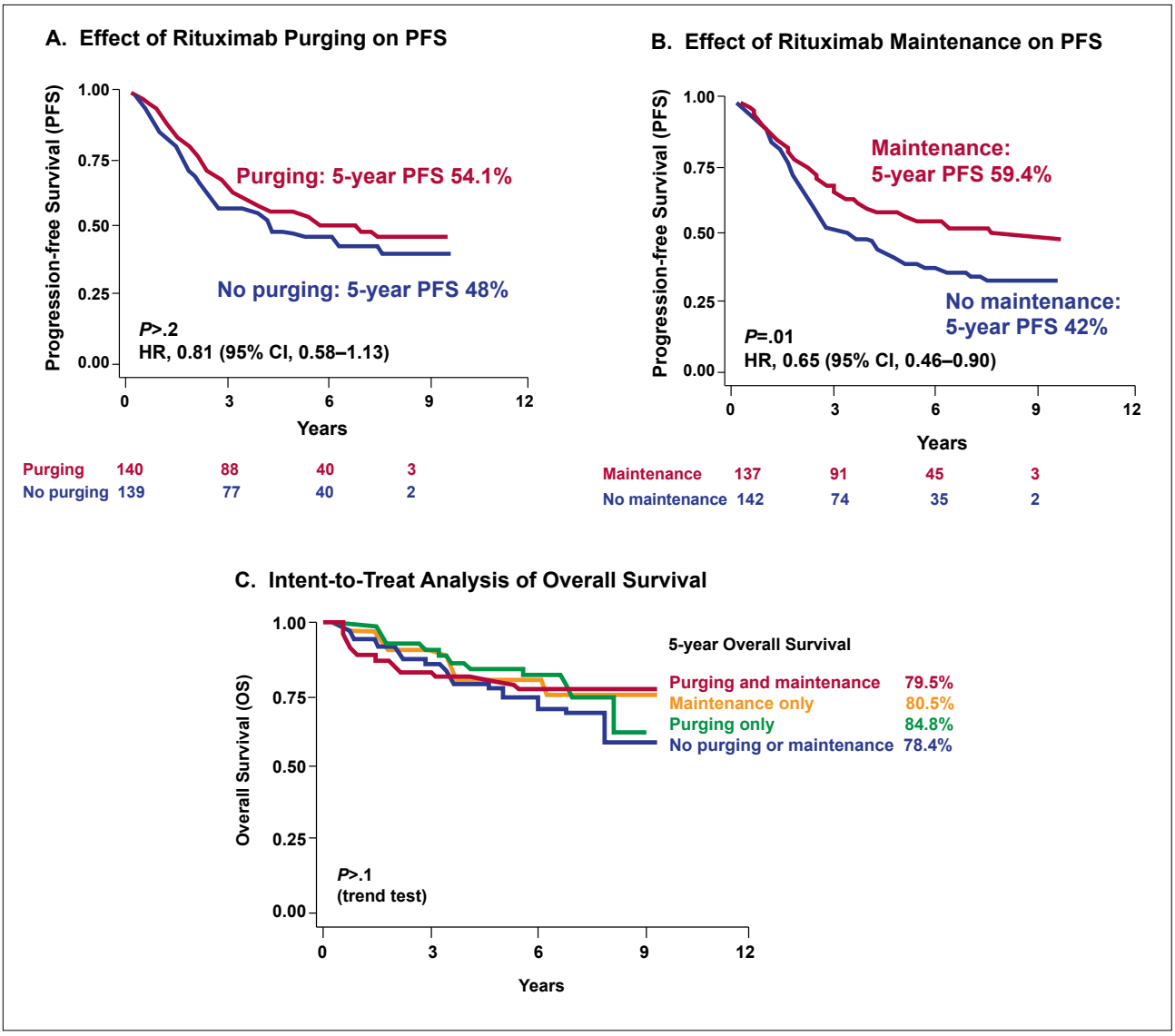

Figure 3. The effects of in vivo purging with rituximab 375 mg/m^2 weekly x 4 and maintenance rituximab 375 mg/m^2 every 3 months for 2 years on progression-free survival (PFS) in patients with relapsed follicular non-Hodgkin lymphoma undergoing high-dose therapy with BEAM (carmustine, cytarabine, etoposide, and melphalan) conditioning.

Data from Pettengell R et al.[10]

for end of treatment response undertaken 4 weeks after therapy ended. The response rates were 17% (3 PR, 6 SD, 7 progressive disease, 2 unknown) and 55% (2 CR, 10 PR, 6 SD, 4 progressive disease) for the LD and HD cohorts, respectively. Dr. Salles noted that 7 of the 24 rituximab-refractory patients (6 in the HD cohort and 1 in the LD cohort) responded. These data support prior studies suggesting that GA101 may offer a viable future therapy, and additional studies are ongoing.

Dr. Mariele Goebeler reported data at EHA on blinatumomab, a CD19/CD3-bispecific antibody construct in NHL patients.[14] Blinatumomab belongs to a new class of constructed monoclonal antibodies known as bi-specific T-cell engagers (BiTEs), which act selectively and direct the human immune system against tumor cells. Blinatumomab specifically targets the CD19 antigen present on B cells, with subsequent downstream adverse effects on cell function.[15] Prior studies demonstrated that blinatumomab delivered by continuous intravenous infusion over 4–8 weeks at doses of 0.015 mg/m^2/day depletes peripheral B cells and induces T effector cell proliferation.[16] Dr. Goebeler provided an update of an ongoing phase I trial in patients with relapsed indolent NHL treated with blinatumomab monotherapy at 60 µg/m^2/day for 4–8 weeks via continuous intravenous infusion. A group of 14 patients (with follicular or

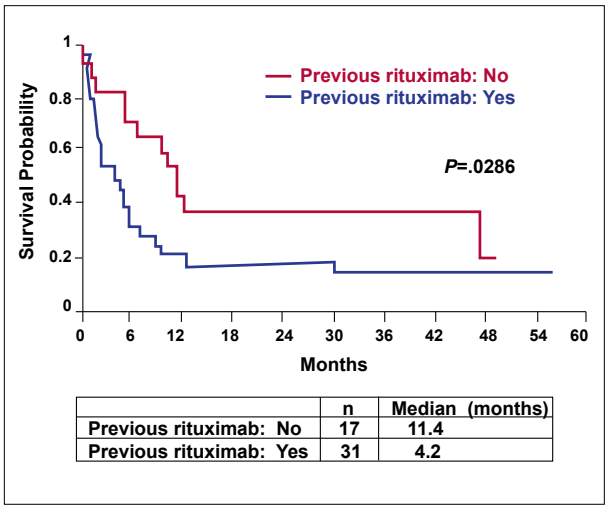

Figure 4. Salvage therapy with rituximab plus gemcitabine and oxaliplatin in relapsed/refractory diffuse large B-cell lymphoma: progression-free survival according to prior rituximab exposure.

Data from Pettengell R et al.[10]

mantle cell histology) were treated, and all 13 evaluable patients showed an objective response (9 PR and 4 CR). As reported in the meeting abstract, as of February 2010, response duration was greater than 27 months, with a median durable response of 13 months. Neurologic symptoms were the most frequent cause of treatment discontinuation, and a predictive biomarker (low peripheral blood B:T cell ratio) was measured to identify patients with a higher frequency of reversible neurologic AEs. A lower initial dose for 1–2 weeks (5 and/or 15 μg/m²/day, n=5 patients) followed by a maintenance dose (60 μg/m²/day) was determined to be able to reduce AEs to allow treatment without interruption. Dr. Goebeler concluded that these promising results confirm single-agent activity with durable effects combined with manageable toxicity. Additional studies in other subtypes of NHL are ongoing, as shown by the presentation of a second study at the EHA meeting describing the induction of complete molecular remissions in patients with persistent and relapsed minimal residual disease–positive B-lineage acute lymphoblastic leukemia.[17]

Table 2. Response to PCI-32765: Preliminary Response Data in Aggressive Lymphoma

A. Response by Dose

Dose Schedule	Dose (mg/kg)	Patients (n)	CR	PR	SD	PD	NE
Daily dosing for 28 days plus 7-day rest period	1.25	7		2	1	4	
	2.5	9		4	1	2	2
	5	6	1	2	1	1	1
	8.3	8	1	2	3	1	1
35 days, no rest period	8.3	10		5	3	1	1
Total (%)		40	2 (5)	15 (37.5)	9 (22.5)	9 (22.5)	5 (12.5)

B. Response by Histology (n=40)

	N	CR	PR	SD	PD	NE*	ORR
Chronic lymphocytic leukemia/ small lymphocytic lymphoma	13	1	8	2		2	69%
Mantle cell lymphoma	4	1	2	1			75%
Diffuse large B-cell lymphoma	6		1	1	4		17%
Follicular lymphoma	13		3	4	4	2	23%
Marginal zone lymphomas	4		1	1	1	1	25%
Total	40	2	15	9	9	5	

CR=complete response; NE=not evaluated; ORR=overall response rate; PR=partial response; PD=progressive disease; SD=stable disease.
*Evaluable responses rate=49% (17/35); Intention to treat response rate=43% (17/40).
Data from Advani R et al.[11]

Table 3. Tumor Response to Aflibercept in Patients With B-cell Lymphoma of Various Histologies*

	Aflibercept Dose Level					
	3 mg/kg (n=3)		6 mg/kg (n=22)		All (N=25)	
Histology	CR	PR	CR	PR	CR	PR
DLBCL	–	–	13	2	13	2
Follicular	3	–	3	2	6	2
MCL	–	–	1	–	1	–
MZL	–	–	1	–	1	–
ALL	3	–	18	4	21	4

*According to Cheson Response Criteria. *J Clin Oncol.* 2007;25:579-586.

ALL=acute lymphoblastic leukemia; CR=complete response; PR=partial response; DLBCL=diffuse large B-cell lymphoma; MCL=mantle cell lymphoma; MZL=marginal zone lymphomas.

Data from Kuhnowski F et al.[18]

The Groupe d'Etude des Lymphomes de l'Adulte (GELA) group presented a second paper at ASCO showing data from a phase I study of aflibercept in combination with R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab) in untreated patients with B-cell lymphoma.[18] Aflibercept is a protein construct made of segments of the extracellular domains of human vascular endothelial growth factor (VEGF) receptors 1 and 2 fused to the constant region (Fc) of human IgG1 with potential antiangiogenic activity. It acts as a soluble receptor, binding to pro-angiogenic VEGFs and preventing them from binding to their cellular target, leading to inhibition of tumor angiogenesis and metastasis.[19] Dr. Haioun, on behalf of GELA, presented the study, in which 25 patients (15 men; median age, 62 years; range, 37–78 years) with B-cell lymphoma received aflibercept (3 mg/kg [n=3] or 6 mg/kg [n=22]) in combination with R-CHOP every 3 weeks (R-CHOP21), for 6–8 cycles. The patients had varied histology, including diffuse large B-cell lymphoma (DLBCL; n=15), follicular lymphoma (n=8), mantle cell lymphoma (n=1), and marginal zone lymphoma (n=1). Ann Arbor stage at diagnosis was I–II (7 patients) or III–IV (18 patients), and 80% of subjects had elevated endogenous VEGF values at baseline. Several biomarkers were also evaluated during the study (eg, endogenous VEGF, CD31, CD34, microvessel density, VEGF receptor, and endothelial progenitor cells). Dr. Haioun reported that aflibercept was well tolerated when combined with R-CHOP; only 1 dose-limiting toxicity at the upper dose level was observed (grade 3 headache and arthralgia). No major AEs were reported; the most frequent treatment-related AE was grade 1/2 reversible dysphonia. CRs were achieved in 21 patients (84%) and PR in 4 patients (3%) (Table 3). At a median follow-up of 18 months (range, 12–24), 1-year PFS was 75.8% (95% CI, 53.8–88.3%). Preliminary data from the analysis of biomarkers indicate that there was no correlation between dose and endogenous VEGF, and there was no evidence of anti-aflibercept antibodies. Dr. Haioun concluded that the results from this study demonstrate that 6 mg/kg of aflibercept in combination with R-CHOP21 is effective and safe, providing further support for a phase III trial to determine the contribution of this agent.

Finally, Dr. Gregor Verhoef reported very early data from a phase II study of the anti-CD22 immunoconjugate inotuzumab ozogamicin (CMC-544) in patients with relapsed/refractory follicular lymphoma.[20] A total of 119 patients were enrolled in this study, which took place in 2 parts: dose escalation to determine the MTD (part 1) and treatment at the MTD (part 2). All patients in part 2 had CD20+/CD22+ NHL and had received prior rituximab therapy. Patients with relapsed follicular lymphoma and DLBCL had received 2 or fewer prior therapies, but they were not refractory to rituximab-containing therapy. Patients classified as having rituximab-refractory "aggressive" NHL could have had DLBCL, mantle cell lymphoma, or transformed follicular lymphoma, with no limit on prior therapies. Patients received 375 mg/m^2 rituximab IV on day 1, followed by 1.8 mg/m^2 CMC-544 on day 2 of each 28-day cycle for up to 8 cycles in the absence of disease progression. The endpoints of the study were safety and efficacy (ORR, OS, and PFS). The pharmacokinetic profile of CMC-544 was also evaluated. Dr. Verhoef reported that the combination of CMC-544 with rituximab had a safety profile very similar to that previously reported for CMC-544 monotherapy. Patients with relapsed follicular lymphoma (n=38) had an ORR of 84%; patients with relapsed DLBCL (n=40) had an ORR of 80%. One-year OS and PFS rates were 97% and 80% (median PFS not reached), respectively, for patients with relapsed follicular lymphoma. One-year OS and PFS rates were 79% and 56% (median PFS of 15.1 months), respectively, for patients with recurrent DLBCL. Patients with rituximab-refractory "aggressive" NHL (n=28) had a lower ORR (18%), with a median PFS of only 1.7 months. It appeared that the extent of prior therapy was the most significant prognostic factor. Therapy was well tolerated; the most common drug-related AEs included thrombocytopenia (46%), nausea (44%), fatigue (40%), and increased aspartate aminotransferase (33%). Finally, there was no pharmacokinetic interaction observed between rituximab and CMC-544.

Diffuse Large B-cell NHL

Dr. Haioun, on behalf of the GELA cooperative group, presented a paper at ASCO that described a study designed to evaluate the efficacy of the combination of

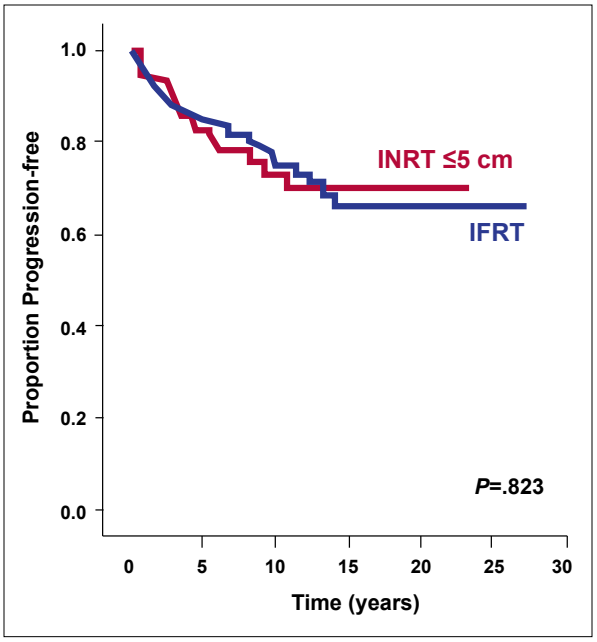

Figure 5. Time to disease progression in 288 patients with limited-stage DLBCL diagnosed between 1981 and 2007 treated with CHOP/CHOP-like chemotherapy and IFRT (pre-1996) or INRT ≤5 cm (post-1996) according to RT field size. Rituximab was included in chemotherapy regimens after 2003.

CHOP= cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL=diffuse large B-cell lymphoma; IFRT=involved field radiation therapy; INRT=involved-node radiotherapy; RT=radiotherapy.

Data from Campbell BA et al.[24]

rituximab with gemcitabine and oxaliplatin (R-GemOx) as salvage therapy for relapsed/refractory DLBCL patients unable to receive high-dose chemotherapy.[21] The rationale for this study is based on the fact that although it has been shown that the addition of rituximab to first-line CHOP improves clinical outcome in DLBCL,[22] treatment options are limited for patients who relapse. High-dose chemotherapy is often unsuitable on the basis of toxicity. However, the less toxic combination of R-GemOx has demonstrated activity as a salvage regimen for relapsed/refractory B-cell lymphoma patients who are not candidates for high-dose therapy (ORR: 82%; median event-free survival: approximately 22 months; median OS: approximately 40 months).[23] Consequently, the current study was designed to determine if this regimen has a role in patients with relapsed/refractory DLBCL patients who cannot receive high-dose chemotherapy. R-GemOx (day 1: rituximab 375 mg/m^2; day 2 gemcitabine 100 mg/m^2, oxaliplatin 100 mg/m^2) was given for 8 cycles every 2 weeks. Patients were evaluated for response after 4 cycles; if a PR or better were observed, consolidation therapy was started for an additional 4 cycles. No dose adjustments were made for hematologic toxicity; instead, the next cycle was delayed until absolute neutrophil count recovery occurred to a level exceeding 1×10^9/L. Dose reduction was allowed for neurotoxicity due to oxaliplatin only. The primary endpoint of the study was ORR at the end of the induction phase; secondary endpoints were ORR at the end of treatment, PFS, OS, and safety. Dr. Haioun reported that a group of 48 patients were enrolled in the study; 36 had completed induction therapy, and 28 had started consolidation (24 completed the entire planned treatment). At the time of the presentation, median follow-up was 41 months (range, 0–57). All the patients had been heavily pretreated (the median number of cycles was 8), and the median time between last therapy and start of R-GemOx was 14 months (range, 1–30 months). Most patients (74%) were at first relapse, only 14% were at second relapse, and 12% had primary refractory disease. The majority of patients (41%) had an IPI score of 4–5; 22% had a score of 2, and 29% had a score of 3. Following induction therapy, 11 patients achieved a CR (23%), 10 achieved an unconfirmed CR (21%), and 8 achieved a PR (17%), yielding an ORR of 60.4% (95% CI, 45.3–74.2%). A further 2 patients had SD, and progressive disease was observed in 5 individuals. Responses at the end of therapy included 11 (23%) CR, 7 (15%) unconfirmed CR, and 4 (8%) PR, yielding an ORR of 45.8% (95% CI, 31.4–60.8%). The therapy was well tolerated; neutropenia was the most common toxicity, but febrile neutropenia was rare, and there were no life-threatening liver, neurologic, or kidney toxicities. The 3-year PFS rate was 20.1% (range, 9.8–32.4%), and the median PFS was 5.3 months (range, 2.6–9.6). OS at 3 years was 28.1% (95% CI, 15.8–41.7%). Patients receiving rituximab prior to R-GemOx salvage had a shorter PFS compared with patients not exposed to rituximab (4.2 vs 11.4 months; P=.0286). Patients who had experienced a delay between last treatment and R-GemOx salvage therapy of less than 12 months had shorter PFS than those whose delay was longer than 1 year (3 vs 10 months; P=.0166). The shortest PFS was seen in patients with previous rituximab exposure and early relapse requiring salvage therapy within 1 year (2 months, P<.0001). Dr. Haioun concluded that R-GemOx had a favorable efficacy and safety profile in relapsed/refractory DLBCL and warrants further clinical investigation.

In relapsed DLBCL patients, fewer than 40% of relapses occur locally. Patients with limited-stage DLBCL frequently receive radiation therapy (RT) at consolidation, the goal being to improve local disease control and minimize toxicity. Dr. Belinda Campbell presented a paper at ASCO that described a study undertaken by the British Columbia Cancer Agency to determine whether there is a role for involved-node radiotherapy (INRT) to

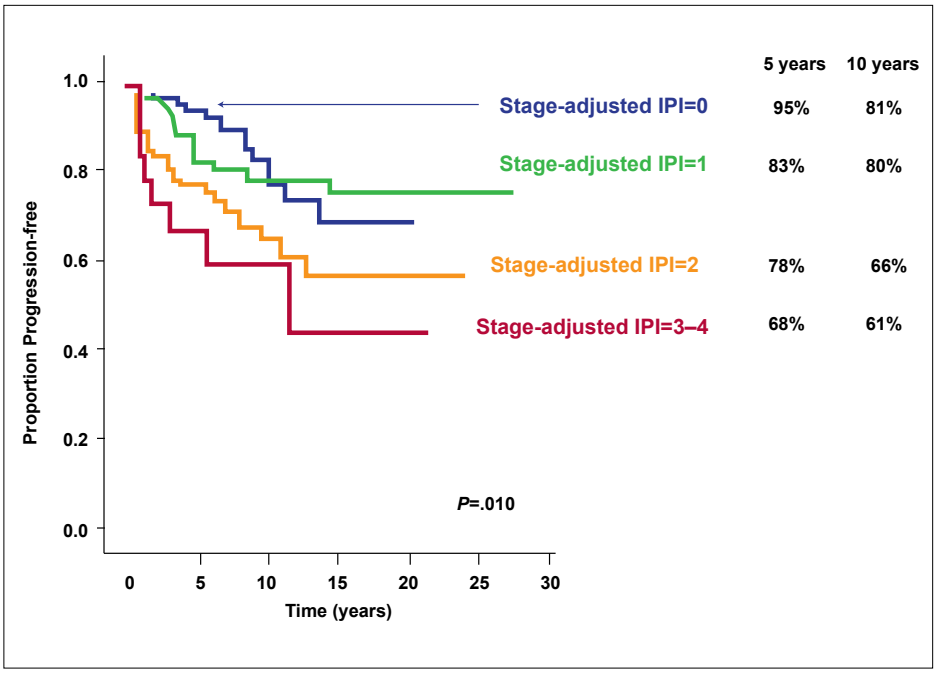

Figure 6. Time to disease progression in 288 patients with limited-stage DLBCL diagnosed between 1981 and 2007 stratified by International Prognostic Index status at study entry. All patients were treated with CHOP/CHOP-like chemotherapy and IFRT (pre-1996) or INRT ≤5 cm (post-1996). Rituximab was included in chemotherapy regimens after 2003.

CHOP= cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL=diffuse large B-cell lymphoma; IFRT=involved field radiation therapy; INRT=involved-node radiotherapy; IPI=International Prognostic Index.

Data from Campbell BA et al.[24]

reduce radiation-induced toxicities and secondary malignancies in long-term survivors of DLBCL, focusing on the influence of RT field size.[24] This retrospective analysis included 288 patients with limited-stage DLBCL diagnosed between 1981 and 2007. Patients with stage III/IV disease, tumor bulk <10 cm, B symptoms, or testicular primary tumors were excluded. All patients had received systemic therapy with 3 cycles of CHOP/CHOP-like chemotherapy, rituximab being added after 2003. Given the time frame of the diagnosis and therapy covered by this analysis, era-specific guidelines for RT changed as follows: prior to 1996, patients were given IFRT; after 1996, they received INRT ≤5 cm (defined as RT to the pre-chemotherapy involved nodes with margins ≤5 cm). Of the 288 patients evaluated, 138 (48%) had received IFRT, and 150 (525) had prior INRT ≤5 cm. Median follow-up was 9.8 and 7.4 years for the IFRT and INRT ≤5 cm groups, respectively. Fifty-six percent of the patients were older than 60 years, 61% were men, and 56% had received RT doses exceeding 35 Gy. The majority of the patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and 55% had extranodal disease. Endpoints of the study were patterns of failure, time to progression (TTP), PFS, OS, and prognostic factors. The median follow-up of living patients was 96 months, and 64 (22%) patients relapsed (32 [23%] in the IFRT group and 32 [21%] in the INRT ≤5 cm group). The most common site of failure was outside the RT field: IFRT 24 (17%), INRT ≤5 cm 26 (17%). After INRT ≤5 cm, marginal recurrence (defined as relapse beyond the INRT ≤5 cm field but within a conventional IFRT field) occurred in 3 (2%) patients. At 5 years, TTP was 84%, PFS was 75%, and OS was 82%, with no significant difference between the 2 RT groups (Figure 5). Long-term follow-up showed a late plateau in TTP: only 2 relapses occurred after 13 years. When TTP was analyzed by stage-adjusted IPI, patients with lower IPI at study entry had significantly more disease-free periods (Figure 6). Age was the only predictive factor of significance for TTP (P=.009) and was also significant for PFS (P<.001), as was performance status (P=.050). RT field size was not a significant predictor for TTP, PFS, or OS. Dr. Campbell concluded that reducing the RT field size to INRT ≤5 cm appears safe, with no adverse effects on clinical outcome as assessed by TTP, PFS, or OS in patients with limited-stage DLBCL treated with combination therapy.

Central Nervous System Lymphoma

High-dose methotrexate is standard frontline treatment for primary central nervous system (CNS) lymphoma, but the acceptance of whole brain radiation therapy (WBRT) in this setting has been controversial. One of the major reasons behind the controversy has been the delayed neurotoxicity frequently observed with this modality.[25] At the ASCO meeting, Dr. Thiel reported results from an 8-year study in 551 immunocompetent patients with newly diagnosed primary CNS lymphoma designed to determine whether the omission of WBRT following induction chemotherapy with high-dose methotrexate has any effect on OS.[26] Patients were randomized to chemotherapy followed by WBRT or chemotherapy alone. After randomization, all patients were scheduled to

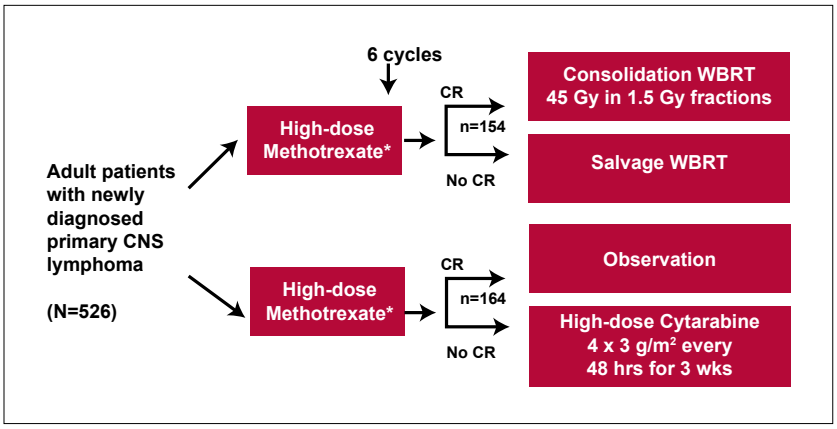

Figure 7. Evaluation of WBRT following frontline chemotherapy for newly diagnosed primary CNS lymphoma: study schema.

CNS=central nervous system; CR=complete response; WBRT=whole-brain radiotherapy.

Data from Thiel E et al.[26]

receive 6 cycles of high-dose methotrexate (4 g/m^2, day 1, biweekly) from 1999–2007 and high-dose methotrexate plus ifosfamide (1.5 g/m^2, days 3–5, biweekly) thereafter. Patients who achieved a CR then received either WBRT (45 Gy in 1.5 Gy fractions) or no further treatment. Patients who did not achieve a CR received salvage WBRT or salvage chemotherapy using high-dose cytarabine (4 × 3 g/m^2/48 hours, for 3 weeks). Of the 551 patients entering the study, 537 (median age, 63 years) received at least 1 course of high-dose methotrexate–based chemotherapy. Of those, 66 died on high-dose methotrexate, 60 dropped out, 411 entered the post–high-dose methotrexate phase, and 318 were treated per protocol. The analysis of the effect of WBRT was based on the hypothesis that WBRT exclusion from first-line treatment for primary CNS lymphoma would not decrease OS and was assessed on a non-inferiority basis. The analysis showed that high-dose methotrexate without WBRT consolidation met the criteria for non-inferiority for OS when compared to high-dose methotrexate plus subsequent WBRT. However, a significantly shorter PFS was observed without WBRT following high-dose methotrexate in the intent-to-treat population and CR subgroup analyses (Figures 7 and 8). In terms of toxicity, delayed neurotoxicity was more frequently observed in the patients who did receive WBRT among patients in CR whether assessed clinically (WBRT [n=45, 48.9%] vs no WBRT [n=33, 28.0%]; *P*=.054) or neuroradiologically (WBRT [n=51, 72.5%] vs no WBRT [n=36, 41.7%]; *P*=.04]). Overall, Dr. Thiel concluded that exclusion of WBRT following high-dose methotrexate for newly diagnosed patients with primary CNS lymphoma does not impact OS, although WBRT is associated with better disease control as evident by prolonged PFS in the intention-to-treat population and CR subgroup analyses.

T-cell Lymphoma

Romidepsin is an histone deacetylase inhibitor that offers potential therapy for cancer patients via the ability to restore normal gene expression that may result in cell cycle arrest, differentiation, and apoptosis. At the EHA meeting, Dr. Bertrand Coiffier presented an analysis of 3 phase II clinical trials including both cutaneous T-cell lymphoma and peripheral T-cell lymphoma patients, representing one of the biggest single-drug evaluations in this disease.[27] Patients with peripheral T-cell lymphoma or cutaneous T-cell lymphoma (N=317) were recruited into 3 phase II multicenter studies (GPI-04-0001, GPI-06-0002, and NCI 1312), and all were included in this analysis. The primary endpoint for the cutaneous T-cell lymphoma studies was ORR assessed by a composite endpoint including skin, blood, lymph node, and viscera involvement. The primary endpoint for peripheral T-cell lymphoma studies was CR. Duration of response and safety were secondary endpoints for all studies. Both populations of patients were of comparable age, heavily pretreated (median 2–4 regimens across all trials), and in advanced stages of their disease (Table 4). The incidence of thrombocytopenia and neutropenia was higher in peripheral T-cell lymphoma patients than in the cutaneous T-cell lymphoma group, reflecting the increased level of bone marrow involvement in peripheral T-cell lymphoma. Overall, however, the therapy was tolerated well, with only 28 patients in each group discontinuing treatment due to AEs (17% and 19% for cutaneous T-cell lymphoma and peripheral T-cell lymphoma, respectively). Romidepsin was effective in both populations; ORR was 34% and 38%, and CR was 6% and 15% for the cutaneous T-cell lymphoma and peripheral T-cell lymphoma patients, respectively. Duration of response was 13.7–15 months across individual trials.

Multiple Myeloma

Induction therapy for multiple myeloma has changed dramatically in recent years for transplant-eligible patients and transplant-ineligible patients. The preferred induction therapy for transplant-eligible patients has evolved

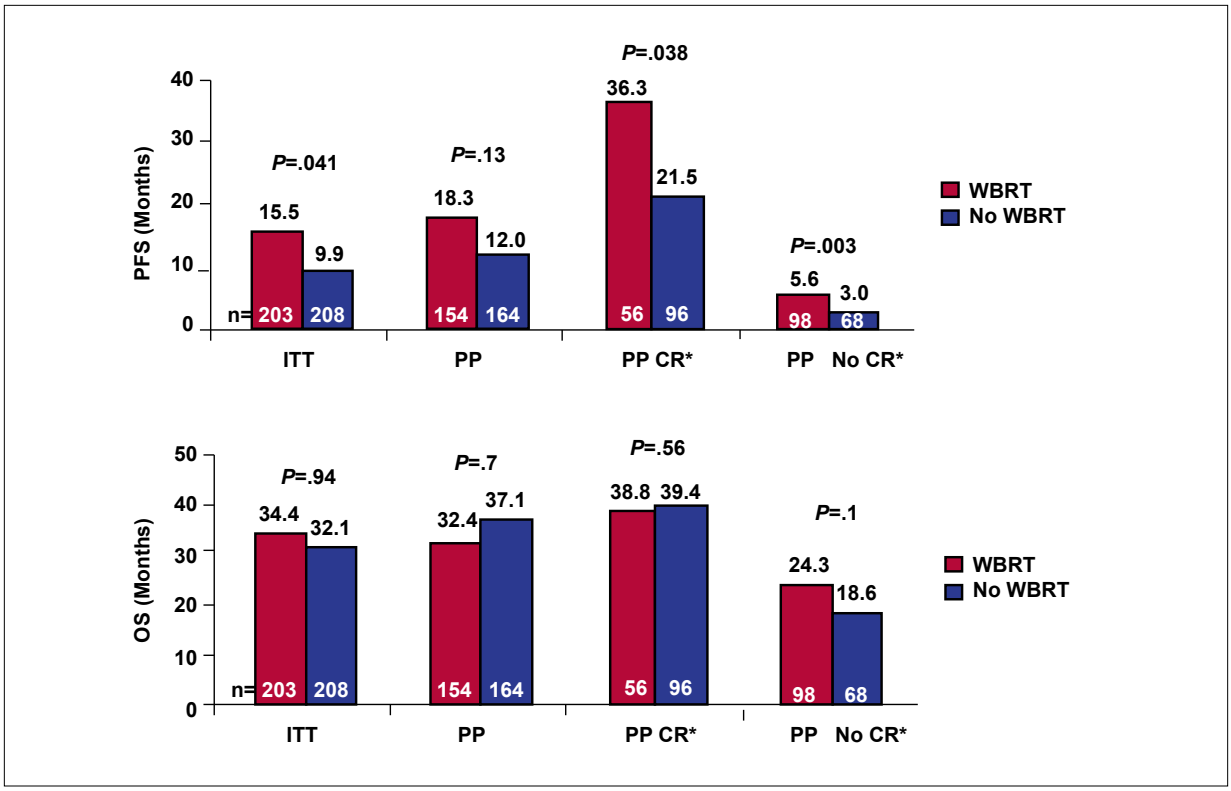

Figure 8. Noninferiority analysis of the effect of WBRT on OS following frontline chemotherapy for newly diagnosed primary CNS lymphoma.

*CR after high-dose methotrexate.

CNS=central nervous system; CR=complete response; ITT=intention to treat; OS=overall survival; PFS=progression-free survival; PP=per protocol; WBRT=whole-brain radiotherapy.

Data from Thiel E et al.[26]

Table 4. Romidepsin Experience in 317 Patients With CTCL or PTCL: A Combined Data Set

	CTCL		PTCL	
Study	**GPI-04-0001 (n=96)**	**NCI 1312 (n=71)**	**GPI-06-0002 (n=103)**	**NCI 1312 (n=47)**
Demographics				
Mean age (range) years	57 (21-89)	56 (28-84)	59 (24-83)	60 (28-84)
Number of prior therapies, median (range)	4 (0-8)	3 (0-7)	2 (1-8)	4 (1-14)
Results				
ORR (CR+PR), n (%)	33 (34%)	24 (34%)	NA	18 (38%)
CR	6 (6%)	4 (6%)	NA	7 (15%)
Median DR (range), months	15 (1-20)	13.7 (1-76)	NA	10 (2-70)

CR=complete response; CTCL=cutaneous T-cell lymphoma; DR=duration of response; NCI=National Cancer Institute; ORR=overall response rate; PR=partial response; PTCL=peripheral T-cell lymphoma.

Data from Coiffier B et al.[27]

from traditional alkylator-based therapy to doublet and triplet combinations of the new immunomodulatory drugs and proteasome inhibitors. For example, thalidomide, bortezomib, and lenalidomide changed frontline therapy in the context of autologous hematopoietic stem cell transplantation (ASCT) as they increased the CR or CR/very good partial response (VGPR) rate before and after ASCT without increasing toxicity.[28] The Intergroupe Francophone du Myelome demonstrated that induction treatment with bortezomib plus dexamethasone (VD) prior to ASCT was superior to VAD (vincristine, doxorubicin [Adriamycin], and dexamethasone) in terms of CR and VGPR assessed before and after ASCT,[29] and impressive data have been reported with the triplet therapy bortezomib, thalidomide, and dexamethasone (VTD).[30,31] However, in these studies, bortezomib-associated peripheral neuropathy was frequent and sometimes severe (9–14% grade 3). At EHA, Dr. Jean-Luc Harousseau described results from a randomized study designed to determine whether VTD was superior to TD in terms of efficacy and safety with a reduced dose of bortezomib. In this study, the Intergroupe Francophone du Myelome compared a regimen of four 21-day cycles of induction with VD (bortezomib 1.3 mg/m^2/day on days 1, 4, 8, and 11 plus dexamethasone 40 mg/day on days 1–4 and 8–11 for the first 2 cycles, and on days 1–4 for the last 2 cycles) with a regimen of VTD (bortezomib 1 mg/m^2/day on days 1, 4, 8, and 11 plus thalidomide 100 mg/d on days 1–21 plus dexamethasone on the same dosing schedule as for VD). Response was assessed after cycles 2 and 4 and following ASCT. Dose adjustments were made in the VTD arm if less than a PR was observed after cycle 2. If there was no peripheral neuropathy, the doses of bortezomib and thalidomide were increased to 1.3 mg/m^2 and 200 mg/day, respectively. Dr. Harousseau reported data from 205 patients ages 65 or younger with newly diagnosed symptomatic multiple myeloma who were randomized at diagnosis (according to β2 microglobulin and presence of del[13] by fluorescence in situ hybridization [FISH]). The patients (N=191) were evaluable for response after cycle 4 (95 patients received VD and 96 received VTD). When the 2 induction therapies were compared, the efficacy results were as follows: CR, 12% versus 14% (*P*=.68), VGPR, 36% versus 50% (*P*=.047), and PR or better, 81% versus 90% (*P*=.09) for VD and VTD, respectively. In 7 cases, the doses of bortezomib and thalidomide were increased due to lack of response in the VTD cohort. The post-ASCT data demonstrated that the combination of reduced-dose bortezomib and thalidomide induces significantly more CR plus VGPR than VD using the normal dose of bortezomib. In addition, even with the addition of thalidomide to the regimen, the incidence of peripheral neuropathy was markedly reduced in the VTD arm (only 3% grade ≥3). Dr. Harousseau concluded that VTD is a candidate for standard of care in the pre-ASCT induction setting for myeloma patients.

A phase III study undertaken by the Italian Multiple Myeloma Network (GIMEMA), presented at the ASCO meeting by Dr. Michele Boccadoro, demonstrated that a 4-drug combination of bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide (VT) was safe and effective for initial treatment of elderly multiple myeloma patients.[32] In this study, 511 patients ages 65 years or older were randomized to receive VMPT followed by VT (n=254) or VMP without maintenance (n=257). The primary endpoint was PFS. Dr. Boccadoro reported that response rates were superior in the VMPT cohort: PR (89% vs 81%; *P*=.01), VGPR (59% vs 50%; *P*=.03), and CR (38% vs 24%; *P*=.0008), respectively. Maintenance therapy with VT did not increase the response to induction. After a median follow-up of 22 months, the 3-year PFS was 60% in VMPT and 42% in VMP (HR, 0.65; 95% CI, 0.48–0.89; *P*=.007). In both arms, PFS was significantly longer in patients who achieved a CR. The presence of chromosomal abnormalities [t(4;14), t(14;16) or del17] did not affect PFS. The 3-year OS was 89% in both groups (*P*=.96). VMPT resulted in higher incidence of grade 3/4 neutropenia (38% vs 28%; *P*=.02) and cardiac complications (10% vs 5%; *P*=.04). The VMPT combination resulted in a higher incidence of AEs, but changing bortezomib dosing to weekly infusion significantly decreased the observed incidence of grade 3/4 peripheral neuropathy (from 18–13% to 4–2%; *P*<.001), without any significant change in CR rates and PFS. This report was the first to show the superiority of a 4-drug combination followed by maintenance in comparison to VMP, and Dr. Boccadoro concluded that the study results demonstrated superior response rates and PFS and manageable toxicity with VMPT-VT.

The role of stem cell transplants in the treatment of multiple myeloma patients was the subject of a paper at ASCO by Dr. Antonio Palumbo, who presented preliminary data from a phase III trial in 402 newly diagnosed myeloma patients that compared melphalan/prednisone/lenalidomide (MPR) with melphalan alone in combination with autologous transplant.[33] All patients received induction therapy with 4 cycles of lenalidomide (25 mg/day for 21 days) and low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22). For consolidation therapy, patients were randomized to receive either MPR (six 28-day cycles; melphalan 0.18 mg/kg days 1–14, prednisone 2 mg/kg days 1–4, lenalidomide 10 mg days 1–21; n=202) or MEL200 (tandem melphalan, 200 mg/m^2 with stem cell support; n=200). The primary endpoint of the study was PFS. Dr. Palumbo reported that PR after induction was 83% and VGPR was 34% overall, which included 6% CR. Overall, the induction therapy was

well tolerated. Both MPR and MEL200 improved the response, although at the time of the meeting, PFS and OS were very similar; PFS at 12 months was 91% for both groups, and OS at 12 months was 97% and 98% for MPR and MEL200, respectively (*P*=.27). Dr. Palumbo noted that there is some evidence of better outcome with the MEL200 regimen, but it appears to be associated with a higher rate of serious side effects.

Two presentations at ASCO provided important evidence that maintenance therapy with lenalidomide improves outcomes for multiple myeloma patients who have received a stem cell transplant. The first presentation, by Dr. Philip McCarthy on behalf of the Cancer and Leukemia Group B (CALGB), ECOG, and the Blood and Marrow Transplant Clinical Trials Network, presented data from a phase III study of lenalidomide compared with placebo maintenance therapy following ASCT in newly diagnosed patients (CALGB 100104).[34] The primary objective of this investigation was to determine whether lenalidomide maintenance impacts TTP following ASCT. Patients with SD were randomized following ASCT to lenalidomide (starting dose 10 mg/day, escalated to 15 mg/day after 3 months) or placebo until disease progression. Dr. McCarthy reported on the second interim analysis of 418 randomized patients, with a median follow-up of 12 months. Median estimated TTP was 25.5 months for the placebo arm, whereas median TTP had not been reached in the study arm. Deaths in both cohorts were similar; 11 and 17 for lenalidomide and placebo, respectively (*P*=0.2), and the number of serious AEs among 210 patients randomized to lenalidomide was 29 compared to 58 among 208 patients randomized to placebo (*P*<.0001). The estimated HR was 0.42 (95% CI, 0.27–0.67), corresponding to a 58% reduction in event risk in the lenalidomide arm. The majority of AEs were hematologic in both arms. Dr. McCarthy noted that results were so favorable in the lenalidomide maintenance cohort therapy that, when given a choice in 2009, many patients in the placebo group elected to switch therapy.

The second presentation on lenalidomide maintenance therapy was by Dr. Michel Attal from Toulouse, France. The study he discussed is very similar in design to the US study but has longer-term data in 614 patients. Dr. Attal reported that with a median follow-up of 24 months from randomization, the first planned interim analysis shows that maintenance with lenalidomide improved 3-year PFS from randomization irrespective of whether patients achieved a CR after ASCT (35% for lenalidomide vs 68% for placebo; $P<10^{-6}$). The study subjects were myeloma patients who received ASCTs followed by consolidation therapy with lenalidomide.[35] As in the US study, maintenance therapy with lenalidomide noticeably reduced the rate of disease progression. Three-year survival was very similar between the cohorts (88% and 80% for lenalidomide and placebo, respectively).

Finally, Dr. Cavo reported the results of an Italian study looking at the impact of frontline bortezomib-based regimens on the clinical outcome of newly diagnosed myeloma patients with high-risk cytogenetic abnormalities.[36] The role of novel agents for the treatment of newly diagnosed multiple myeloma patients with high-risk cytogenetic abnormalities [t(4;14) and/or del(17p)] is worth study since these patients have a poorer prognosis and typically fail to respond well to traditional therapy. Many believe that it is critical to be able to identify a patient's chromosomal abnormalities prior to starting therapy to allow individualized treatment. However, clinical studies have demonstrated that at least for bortezomib, patients with and without such genetic profiles tend to respond to the same extent.[37] The goal of the study was to determine what impact, if any, high-risk chromosomal abnormalities exert on patient outcome. Dr. Cavo and colleagues analyzed the CR and PFS rates of 587 newly diagnosed patients who received bortezomib as part of their upfront therapy in 1 of 3 regimens: VTD, VMP, or VMPT. Patients were assessed by interphase FISH analysis to determine their cytogenetic status. Three profiles were identified: patients with no chromosomal deletions (n=261), those with del(13q) alone (n=174), and those with t(4;14) and/or del (17p) (n=152). Dr. Cavo reported that there was no statistically significant difference in CR rates between patients identified as high risk and those lacking the cytogenetic abnormalities t(4;14) and/or del (17p) (38.1% vs 32.5%; *P*=.02) or those who carried del(13q) alone (46.5%; *P*=.1). However, the CR rate reported for the group of patients with del(13q) alone was significantly higher than that observed for patients lacking chromosomal abnormalities; 47% versus 33%, respectively (*P*=.003). In addition, PFS rates at 30 months post-treatment were similar for both groups; 62% for high-risk patients compared to 66% for those without chromosomal abnormalities (*P*=.06) versus 64% for del(13q) alone. In the subgroup of patients with translocations between chromosomes 4 and 14 and/or a deletion within chromosome 17, a direct comparison of response revealed that patients with the del(17p) mutation had a lower chance of achieving a CR than the t(4;14) carrying patients (28.3% vs 47.6%; *P*=.02). In contrast, PFS at 30 months post-treatment was similar for both groups: 66% versus 69% (*P*=.3) for del(17p) and t(4;14) respectively. Dr. Cavo concluded that although the results of this study are consistent with the observation that high-risk patients can respond similarly to bortezomib as patients without chromosomal abnormalities, the results of this analysis should not be over-interpreted but used to guide further evaluations in larger groups of homogeneously treated patients. It may then be possible to draw firm con-

clusions about the utility of bortezomib-based regimens to overcome the adverse prognosis related to the presence of t(4;14) and/or del(17p). Ultimately, it may be possible to stratify patients and choose optimal treatment on the basis of their chromosomal abnormalities.

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Commentary

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After I perused the abstract books from ASCO and EHA prior to the meetings, a number of questions warranted answers from the presentations. Perhaps the most important was whether maintenance rituximab should be standard for follicular lymphoma. The issue had been quite controversial. Of the various studies of maintenance following chemotherapy or following rituximab induction, none demonstrated a survival advantage. However, there was, as yet, no study of maintenance in the frontline setting following what would be considered standard of care—chemotherapy plus rituximab. Lymphoma experts had long awaited the results of the Primary Rituximab and Maintenance (PRIMA) trial, in which previously untreated patients with follicular lymphoma who were thought to require treatment received either R-CHOP, R-CVP (rituximab, cyclophosphamide, vincristine, and prednisolone), or R-FCM (rituximab, fludarabine, chlorambucil, mitoxantrone) according to investigator choice, and those that did not progress following treatment were randomized to rituximab maintenance every 2 months for 2 years. Dr. Gilles Salles provided data on the 1,217 patients entered into the trial, 1,018 of whom were randomized.[1] Maintenance significantly reduced the risk of lymphoma progression, with a PFS of 82% versus 66% at 24 months (HR, 0.50 [*P*<.0001]), with only a modest increase in adverse events. The benefit appeared to hold for all subgroups analyzed.

In a second study, Dr. Ruth Pettengell, representing the European Bone Marrow Transplant Lymphoma Working Party, presented a randomized study of rituximab as in vivo purging and/or as maintenance in patients with relapsed or refractory follicular lymphoma undergoing autologous stem cell transplantation.[2] The group receiving rituximab in both strategies experienced a longer PFS than the groups receiving maintenance only, purging only, or neither. However, there was no survival benefit from any approach.

Dr. Richard Fisher, the discussant for these abstracts, concluded that these data supported the use of maintenance rituximab in all patients with follicular lymphoma. As much as I hate to disagree with my very good friend, my impression was more tempered. The reasons are several: we still do not know which of the half-dozen maintenance schedules out there is optimal (frequency, duration), maintenance incurs increased cost, and it is associated with toxicities, notably neutropenia and infections. Several previous studies have demonstrated that retreatment upon relapse is associated with an outcome comparable to maintenance, and there are concerns that progression during or within a short time following maintenance may confer an adverse outcome, at least precluding further rituximab therapy. Importantly, no study has yet demonstrated a survival advantage. The National Lymphocare Study update at the ASCO meeting revealed that 55% of physicians already use maintenance,[3] and I suspect this figure will increase substantially following ASCO. As for me, I am not yet using this approach.

The role of radiation in several lymphoma settings was also evaluated. Campbell and coworkers from the British Columbia Cancer Agency conducted a study in patients with limited-stage DLBCL.[4] After chemotherapy alone, more than 40% of patients relapse locally. However, radiation can have adverse effects as well. Thus, Campbell and coworkers sought to determine if INRT could be as effective as IFRT, but with fewer toxicities, notably secondary malignancies. Indeed, in this nonrandomized study, the outcomes with the 2 approaches appeared comparable. However, whether there is any role for INRT needs to be viewed in the context of other studies that directly examined the role of radiation therapy. In a GELA trial, 576 patients were randomized to 4 cycles of CHOP chemotherapy with or without IFRT, and the event-free survivals were the same in both treatment groups.[5] A similar conclusion was drawn from an ECOG 1484 study, in which patients in remission following 8 cycles of CHOP were randomized to low-dose IFRT or observation.[6]

Thiel and associates[7] conducted a large, randomized study evaluating the role of WBRT in primary CNS lymphoma in immunocompetent patients. Whereas high-dose methotrexate is the standard of care, the contribution of WBRT is controversial because of its potentially devastating consequences. In this large, randomized trial, there was no clear benefit for WBRT in patients who did or did not achieve a CR with induction chemotherapy, yet the increase in neurotoxicity was substantial. Newer options are clearly needed for this unfortunate group of patients.

A group of patients that represents an unmet need are those with relapsed or refractory DLBCL who are not candidates for high-dose therapy or stem cell transplant. The GELA group presented their data with rituximab, gemcitabine, and oxaliplatin in 49 patients, only half of whom completed the intended 8 cycles.[8] The response rate after 4 cycles was 60%, including 23% CRs; however,

after the 8 cycles, the response rate decreased to 46% (with 23% CR). Importantly, the PFS was a disappointing 4 months in patients who had received prior rituximab, as almost all patients now do. Another regimen of potential interest is R-bendamustine, which induced an 80% response rate with 60% CRs as the initial treatment of elderly patients with DLBCL.[9] This regimen therefore might be effective in the relapsed and refractory setting.

What we clearly need are newer and more effective agents with less toxicity. Numerous monoclonal antibodies, including 10 directed at CD20, are in clinical trials. Beyond traditional monoclonal antibodies are radioimmunotherapeutics, bi- and tri-specific antibodies, small modular immunopharmaceuticals, immunotoxins, and drug antibody conjugates. A number of drug-antibody conjugates (DAC) are of interest. Response rates of 40–50% with the DAC SGN-35 in relapsed/refractory HL have stimulated interest in the incorporation of this agent into combinations.[10] Response rates of 80% have been reported in patients with follicular lymphoma or DLBCL with the combination of rituximab and the DAC anti-CD22 inotuzumab ozogamicin.[11] BiTE, a CD19/CD3 construct, had demonstrated impressive activity in the initial phase I trial, but with an unacceptable risk of toxicities, including encephalopathy.[12] Subsequent studies using a different schedule of administration showed activity without the previous AEs. Further development of this promising agent is warranted in NHL and acute lymphoblastic leukemia.

Other novel drugs target various intracellular pathways. One important pathway is initiated by the B-cell receptor (BCR), which through non–ligand-dependent activation activates a series of events that leads to lymphoma expansion and proliferation. One important component of the pathway is spleen tyrosine kinase (Syk). Friedberg and coworkers[13] previously demonstrated activity for fostamatinib disodium, which inhibits Syk, in patients with a variety of lymphoma histologies. At ASCO, Fowler and coworkers[14] presented their data from an ongoing phase I trial of PCI-32765, an oral drug that targets Btk. Mutations of Btk prevent B-cell maturation, and its inhibition blocks BCR signaling and induces apoptosis. The response rate of 40% for this oral agent is very promising. The GELA group also presented data with the VEGF Trap aflibercept in combination with chemotherapy in a phase I trial. High response rates that were reasonably durable were reported, but they were difficult to interpret without a randomized comparison.[15] Another agent of interest is CAL-101, which targets the 110∂ isoform of AKT; it induced responses in about half of patients with a variety of histologies of relapsed and refractory lymphomas.[16] How best to incorporate these new agents into novel treatment strategies is a topic of considerable discussion.

The availability of FDG-PET has markedly altered how we evaluate patients with lymphoma. Although this technique is not currently a part of staging, a workshop will be held at the 2011 International Conference on Malignant Lymphoma in Lugano to determine whether a modification of current Ann Arbor staging is warranted. PET is important in the restaging of the curable lymphomas, HL, and DLBCL. Although PET is being increasingly ordered after 1 or more cycles of therapy to serve as an early predictor of patient outcome, interim PET does not appear to add to post-therapy PET in patients with DLBCL, and its use is discouraged.[17] However, it may play a greater role in HL. Gallamini and coworkers[18] previously demonstrated that PET after 2 cycles was a much stronger predictor of outcome than the IPI, although it is not clear whether changing therapy on the basis of these results will improve patient outcome. At ASCO, Gallamini presented a retrospective analysis of patients with a positive scan after 2 cycles of ABVD, in whom treatment was changed from ABVD to escalated BEACOPP (× 4)/standard BEACOPP (× 4). Outcome in these patients was superior to what would be expected for patients remaining on ABVD and closer to that of patients with a negative scan.[18] Several US and international trials are attempting to prospectively validate this concept, reducing therapy in low-risk patients while augmenting treatment in those with a high risk.

HL is one of the major successes of modern hematology/oncology, and long-term complications of treatment have become a greater concern than disease recurrence. The German Hodgkin's Study Group, which has conducted some of the most important studies in these patients, presented the updated results of their HD10 trial. In patients with early-stage, favorable disease, 2 cycles of ABVD with only 20 Gy of IFRT is their new standard, with comparable efficacy to more cycles of chemotherapy and higher doses of RT, but with a reduced likelihood of long-term treatment-related complications.[19] Whether low-risk patients can be completely spared radiation is the subject of a number of ongoing trials.

Nevertheless, many patients still fail to respond to initial treatment or relapse following induction or salvage stem cell transplantation. New agents in clinical trials for this patient population include bendamustine, lenalidomide, the mammalian target of rapamycin inhibitor everolimus, and the DAC SGN-35. At the ASCO meeting, Sureda and coworkers[20] presented interesting results with the histone deacetylase inhibitor panobinostat. The eventual goal would be to integrate

the most effective of these agents into an initial approach for high-risk patients.

Novel agents have also altered treatment paradigms in other hematologic malignancies. The second-generation BCR-ABL kinase inhibitor dasatinib was shown to be more effective than imatinib, the drug that completely changed our approach to the disease.[21] New regimens for the initial treatment of patients with multiple myeloma—including bortezomib, lenalidomide, and thalidomide with dexamethasone—have increased response rates to 90%. Two studies presented at the ASCO meeting supported an improvement in survival with the use of lenalidomide as maintenance.[22,23] These new and more effective approaches bring the role of stem cell transplant into question.

What I learned at the ASCO and EHA meetings was that treatment paradigms in lymphoma, chronic lymphocytic leukemia, and multiple myeloma are changing. Perhaps, with the myriad targeted agents, we can envision a time when we can eliminate cytotoxic therapy altogether, reducing toxicity while realizing the goal of cure for these patients.

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