Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

October 2011 | A SPECIAL MEETING REVIEW EDITION | Volume 9, Issue 10, Supplement 24

Highlights From the Pan Pacific Lymphoma Conference

August 15–19, 2011
Kauai, Hawaii

Special Reporting on:

- Aggressive T-Cell Lymphomas
- Novel Agents With Activity in CLL/SLL
- PTCL—Update on Novel Therapies
- Agents Targeting the Stromal Elements of the Lymph Node
- Inducing Apoptosis in Lymphoma Cells Through Novel Agents

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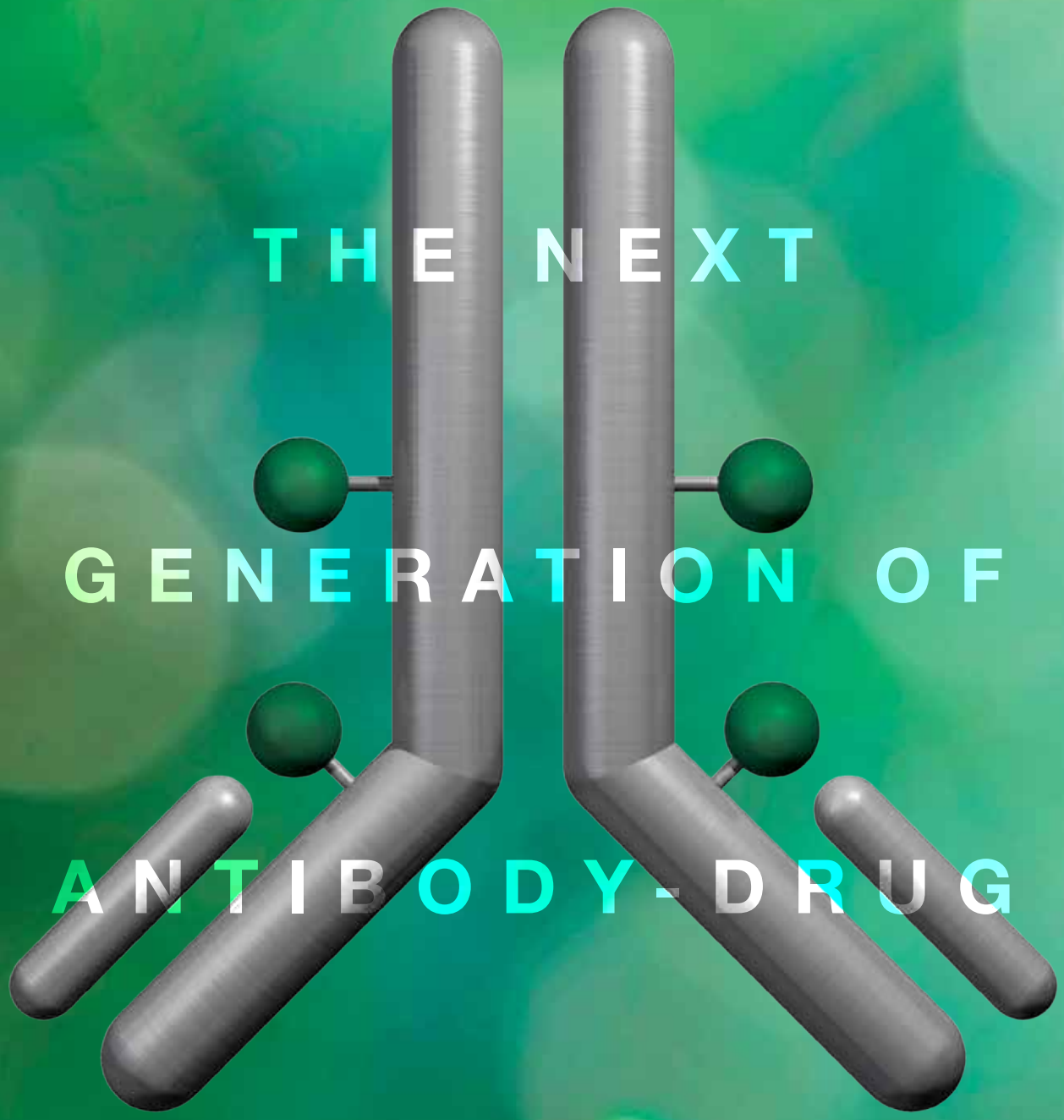
ENGINEERING THE NEXT GENERATION OF ANTIBODY-DRUG CONJUGATES



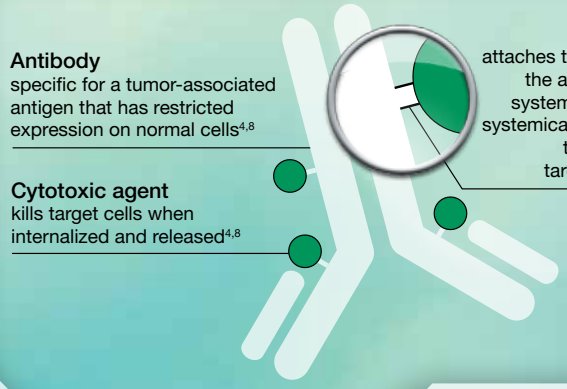
An innovative approach to improving outcomes in patients with cancer

Antibody-drug conjugates (ADCs) use a conditionally stable linker to combine the targeting specificity of monoclonal antibodies with the tumor-killing power of potent cytotoxic agents.[1,2] This could allow potent drugs to be delivered directly to tumor cells with minimal systemic toxicity.

Optimizing the parameters for clinical success

Scientists at Seattle Genetics are focused on parameters critical to the effective performance of ADCs, including target antigen selection,[3,4] linker stability[5-7] and potent cytotoxic agents.[4,7,8]

Elements of an antibody-drug conjugate



ADCs link precision and potency for greater activity

A preclinical (in vivo) study demonstrated that the ADC is more active than the antibody alone (mAb) or the admixture (mAb + cytotoxic agent unlinked)[10]

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Aggressive T-Cell Lymphomas

Dr. Andrej R. Shustov discussed aggressive T-cell lymphomas at the 2011 Pan Pacific Lymphoma Conference.[1] The World Health Organization (WHO) recognizes 3 subfamilies of peripheral T-cell lymphoma (PTCL): extranodal, nodal, and leukemic T-cell lymphomas. Nodal disease is the most common, and among these the most common is PTCL not otherwise specified (NOS), followed by angioimmunoblastic T-cell lymphoma, extranodal NK-/T-cell lymphoma (nasal type), adult T-cell leukemia/lymphoma, and anaplastic large cell lymphoma (ALK-positive and ALK-negative).[2] These subtypes account for approximately 90% of all PTCL patients.

Diagnosis can be challenging because most types of T-cell lymphoma do not have a specific immunophenotype. Therefore, a correct diagnosis requires a combination of molecular analysis, clinical presentation, morphology, and genetics. The incidence of PTCL varies geographically and appears to be increasing.[3,4] The clinical outcomes critically depend on the T-cell lymphoma subtype, but in most subtypes, the outcomes are generally poor. Fewer than 30% of patients with the most common subtypes remain alive 5 years after diagnosis.[2] In addition to disease subtype, international prognostic index (IPI) scores factor into a prognosis.[5]

Attempts were made to improve outcomes in patients with PTCL by applying consolidated high-dose therapy and autologous hematopoietic stem cell transplantation. However, several phase II studies examining this treatment show very modest overall survival (OS), suggesting that this treatment is not very effective for PTCL. A study of 83 patients by Reimer and colleagues suggests that patients with high IPI/prognostic index for PTCL (PIT) in particular may not benefit from high-dose therapy/autologous hematopoietic stem cell transplantation, with 3-year progression-free survival (PFS) of 36%.[6]

In the NLG-T-01 trial, 121 patients (median age, 55 years) received cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP) therapy every 14 days for 3 cycles. Patients with a complete response (CR) or partial response (PR) then received another 3 cycles of CHOEP every 14 days. Patients who still showed a CR or PR then underwent stem cell collection and beam-supported autologous large stem cell transplant.[7] The subgroup of 21 patients with enteropathy-associated T-cell lymphoma, who usually have extremely poor outcomes, showed a 5-year OS rate of 44% and 5-year PFS rate of 40%. Patients with PTCL unspecified (n=62) showed a 5-year OS of 45%, although 5-year PFS was only 34%.

Despite these encouraging results, several studies suggest that allogeneic transplant may be preferable to autologous transplant for patients with high-risk disease. In a study by Le Gouil and colleagues, although treatment-related mortality was 34%, the 5-year OS was close to 60% for patients with PTCL who underwent allogeneic stem cell transplantation.[8]

Very encouraging early results were also obtained by Corradini and colleagues using non-myeloablative allogeneic transplant, with 5-year OS and 5-year PFS of 80% and 64%, respectively, with survival curves showing a clear plateau.[9] Finally, a study of 17 patients with multiple PTCL histologies, and 5 patients with refractory disease at the time of transplant, showed a 3-year OS of 59% and 3-year PFS of 53%.[10] Thus, for selected patients, allogeneic transplants might provide long-term control of the disease and possibly cure the drug-resistant lymphoma effect.

The last few years have seen the development of some promising new

therapies based on selective targeting of specific cellular pathways. Pralatrexate is a novel antifolate that inhibits the activity of dihydrofolate reductase (DHFR), with a mechanism of action similar to that of methotrexate. Once internalized, the molecule is glutamated, which prevents its escape from the cell. PROPEL (Pralatrexate in Patients With Relapsed or Refractory Peripheral T-cell Lymphoma) was the first large, prospective, multicenter, single-arm, open-label, international trial conducted for relapsed/refractory PTCL.[11] This pivotal phase II study had 109 evaluable patients with histologically confirmed PTCL. Pralatrexate (30 mg/m^2) was administered intravenously for 6 weeks, followed by 1 week of rest. The overall response rate (ORR) was 29%, including 12 patients (11%) with a CR or unconfirmed CR (CRu), and 20 patients (18%) with a PR. The median duration of response was 10.1 months, and median OS was 14.5 months.

Romidepsin (depsipeptide) is a histone deacetylase (HDAC) inhibitor. HDACs modify histone chemistry, which in turn modulates gene activity. Several phase II, multicenter, international, single-arm studies have examined romidepsin in cutaneous T-cell lymphoma (CTCL) and/or PTCL. Two trials conducted by 2 separate organizations that examined romidepsin in CTCL patients yielded similar results. Trial GPI-04-001 enrolled 96 patients with CTCL, and trial NCI1312 enrolled 71 patients with CTCL, plus 47 patients with PTCL. The trials yielded similar ORRs of 34% and 35%, respectively, in CTCL patients. GPI-06-0004, which enrolled 131 patients with PTCL and treated 130, served as grounds for approval of romidepsin in PTCL. In the study, 19 CRs (15%) and 14 PRs (10%) were observed, producing an ORR of 25%. The median duration of response was 17 months (range, 1–34). Some patients with refractory disease may show a response to romidepsin after only 1 or 2 cycles.

Dr. Shustov also presented updated results from a phase II study in patients with relapsed or refractory systemic anaplastic large cell lymphoma treated with brentuximab vedotin (SGN-35).[12] Brentuximab vedotin is an anti-CD30 antibody conjugated to the potent antitubulin agent monomethyl auristatin E, which induces cell cycle arrest and apoptosis in cells that internalize the antibody. The study enrolled 58 patients, of whom 72% had ALK-negative disease and 62% were refractory to frontline treatment. The study showed an ORR of 86%, including 57% CR and 29% PR. The median duration of response was 12.6 months, median PFS was 13.3 months, and median OS was not reached at the time of the analysis. Of the 57 evaluable patients, 56 (97%) showed a tumor response. As with romidepsin, some patients treated with brentuximab vedotin may show a very rapid response to treatment.

Other promising novel agents and strategies are in development. An anti-CD45 antibody conjugated to iodine-131 is being used in conjunction with autologous transplant.[13]

What Are the Newer Agents That Have Clinical Activity in MCL?

Dr. Jonathan W. Friedberg reviewed new agents under investigation in mantle cell lymphoma (MCL).[1] Although bortezomib is already approved for treating MCL, newer agents and novel combinations are showing promising activity that could surpass that of bortezomib. A phase II study enrolled patients with relapsed, indolent B-cell lymphoma or MCL. Patients received bendamustine (90 mg/m^2, days 1 and 4), rituximab (375 mg/m^2, day 1), and bortezomib (1.3 mg/m^2, days 1, 4, 8, and 11). The 7 MCL patients had an overall response rate (ORR) of 71% (range, 36–92%). In comparison, the pivotal trial of bortezomib monotherapy yielded an ORR of 32%.[2] Median progression-free survival with the combination therapy was approximately 23 months,[3] and the combination was reasonably well tolerated, with 63% of patients completing all 6 treatment cycles. Lenalidomide has shown activity against MCL,[4] although the mechanism of action remains poorly understood. An international trial included 57 MCL patients and yielded an ORR of 42%. Response duration appears durable. A randomized phase II study designed to examine the combination of lenalidomide plus rituximab is enrolling patients older than 65 years with newly diagnosed MCL. Carfilzomib is a newer antiproteasome that appears to have stronger activity compared to bortezomib and could circumvent the neuropathy that is associated with bortezomib. Dr. Friedberg also reviewed data in MCL patients showing that inhibition of the B-cell receptor pathway is another promising approach for this disease, based on small studies. Bruton's tyrosine kinase and phosphatidyl inositol 3-phosphate are particularly attractive targets for MCL, and appear to have reduced toxicity compared to standard chemotherapy.

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Alemtuzumab is an anti-CD52 antibody that was used to purge circulating tumor cells prior to autologous transplant[14]; however, the patient succumbed to very severe viral infections post-transplant, necessitating reevaluation of the pretransplant protocol.

In summary, no optimal frontline regimen has been identified for patients with PTCL, nor has the role for autologous transplant been established. Anthracycline-containing regimens remain the most commonly used for initial PTCL therapy. However, a retrospective analysis by the International T-cell Lymphoma project suggests that anthracyclines may not significantly improve outcomes in PTCL NOS and angioimmunoblastic T-cell lymphoma (and possibly other subtypes).[1] Therefore, the use of anthracyclines as frontline treatment remains open to discussion.

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Should PET Scanning Be Used to Direct Therapy for Advanced Hodgkin Lymphoma?

Dr. Oliver W. Press discussed the use of positron emission tomography (PET) in Hodgkin lymphoma (HL).[1] Based on studies by Cheson and colleagues, PET is currently recommended in large cell lymphoma and HL for staging and post-treatment disease assessment.[2,3] Outside of the clinical trial setting, PET is not currently recommended for indolent lymphomas or those that show variable avidity to fluorodeoxyglucose (FDG), such as marginal zone lymphoma or peripheral T-cell lymphoma.

In contrast, the National Comprehensive Cancer Network guidelines currently recommend restaging with PET or computed tomography (CT) scan for early stage, favorable HL following the first 2 cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) therapy, and for stage III/IV HL after 2–4 cycles.[4] A compilation of studies shows that although PET and CT scans show excellent sensitivity and specificity, PET consistently appears superior in these measures.[3] When used for staging HL, PET can result in upstaging for up to 25% of patients,[3] which is particularly important for patients with HL.

A more pressing and controversial issue currently is whether PET or CT imaging may be used for interim response evaluation during induction therapy. Possible advantages of interim scanning include identification of patients who are very likely to be cured with induction therapy, so that treatment could potentially be reduced, or identifying patients who are likely to fail therapy, so that treatment could potentially be escalated. Key issues for interim PET/CT imaging include standardization of protocols and scan interpretation. Results are affected by technical details including the FDG dose, the patient's blood sugar level, and the amount of time that elapses

after injecting the patient with FDG, prior to performing the scan. Scan interpretation can be made more consistent by using the London/Deauville 5-point scale to guide whether a PET scan is positive or negative.

Dr. Press also noted that, although there is evidence suggesting that other measures, such as standardized uptake value (SUV), may offer some improvements over visual assessment, the latter is the current standard. Several studies show that approximately 75–80% of patients will become PET-negative after 2 treatment cycles, and virtually all of these patients do well. A 2007 study by Gallamini and colleagues with 260 patients showed that patients whose disease was PET-negative after 2 treatment cycles had a drastically superior 5-year survival compared to patients who were still PET-positive.[5] The survival rates were not affected by international prognostic scores of 0–2 versus 3–7. A follow-up study with 261 patients showed similar results.[6] Failure-free survival (FFS) was related to negative versus positive PET results after 2 treatment cycles, regardless of IPS prognostic scores.

A pediatric study also investigated the relationship between early response as detected by imaging and event-free survival (EFS). In patients who were both PET- and CT-negative, 3-year EFS was 56% (n=43), whereas patients with a response confirmed by both scans had 3-year EFS of 90% (n=469).[7]

While the above results show that early scanning can be correlated to long-term outcomes, interim scanning would be most valuable if the results could be used to improve therapy. Supporting this line of reasoning, a retrospective study by Gallamini and colleagues suggests that, following a PET-positive scan after 2 cycles of ABVD therapy, switching to bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine hydrochloride, and prednisone (BEACOPP) can improve the rate of FFS.[8] However, prospective, randomized studies are clearly needed, and several ongoing trials are examining the use of interim PET or CT scanning for patients with early stage or advanced HL. The S0816 Intergroup trial in advanced HL involves the Southwest Oncology Group (SWOG), the Cancer and Leukemia Group B (CALGB), and the European Cooperative Oncology Group (ECOG). Designed to enroll 200 patients, the study will initially stage patients' disease with PET or CT. After 2 cycles of ABVD chemotherapy, another PET or CT scan will be performed. Patients who are PET-negative will receive another 4 cycles of ABVD, followed by a third PET or CT scan. Patients with PET-positive disease after the second scan will receive 6 cycles of escalated BEACOPP (if they are HIV-negative) or 6 cycles of standard BEACOPP (if they are HIV-positive). All patients will then be examined by a third PET or CT scan.

Finally, PET scanning may be used for end-of-treatment restaging, and several studies have shown high negative and positive predictive values for PET in this setting.[3] Study HD15 by the German Hodgkin Study Group (GHSG) randomized patients with advanced HL to 1 of 3 treatment regimens of BEACOPP. Patients with a PR plus residual disease including a residual mass of at least 2.5 cm received a PET scan. Patients who were PET-positive

The Spectrum of Cutaneous T-Cell Lymphomas: Standard and Novel Therapies

Dr. Steven M. Horwitz reviewed standard and novel therapies for cutaneous T-cell lymphomas (CTCL), emphasizing non–mycosis fungoides (MF) subtypes.[1] Management of these diseases poses a challenge because prospective studies are lacking in most of the rare T-cell entities. CTCL subtypes can be distinguished between those that are more similar to MF, which tend to have a more indolent course, and those that are less similar, which tend to be more aggressive. Clinical studies that are planned or in progress will examine the immunoconjugate brentuximab vedotin in patients with lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma, both of which are CD30-positive diseases with a non-aggressive course. In contrast to patients with MF, patients with CTCL require a complete work-up to determine the correct treatment. They should undergo laboratory studies and imaging; patients with aggressive histologies, who might require an aggressive approach, should undergo bone marrow analysis.[2] Treatment strategies for non-MF CTCL can be divided based on indolent versus aggressive disease. For solitary or regional disease, local excision and/or radiation are appropriate. For more widespread disease, biologic therapies are an option, but chemotherapy may be appropriate for more aggressive disease. For aggressive CTCL, such as primary gamma-delta, CD8-positive epidermitropic, or blastic NK types, aggressive chemotherapy followed by allogeneic stem cell transplant may be appropriate for younger patients. Single-agent chemotherapy is an option for treating with palliative intent, and clinical trials should be considered.

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then received radiotherapy to the residual masses. This strategy reduced the use of radiation after chemotherapy to 11%. In contrast, in an earlier study (HD9) by the same group, 70% of patients had received radiotherapy. The treatment strategy yielded excellent results based on time to progression in patients who were PET-negative, and therefore did not receive radiation, and in patients who were PET-positive and received radiation therapy. PET scanning has also been examined for serial monitoring of patients in remission. However, of the few studies that exist, one showed a positive predictive value of only 23%, and the cost for detecting an event was $100,000.[9]

Currently, PET clearly can be used for baseline staging and end-of-treatment evaluation. However, the best use of interim PET remains to be determined, and PET is not recommended for serial monitoring. Further information will be forthcoming as results from ongoing clinical trials become available.

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Targeting the Stroma/Microenvironment in Lymphoma

Dr. Andre H. Goy discussed agents targeting the stromal elements of the lymph node.[1] Dr. Goy noted that the microenvironment is now understood to be a key player in lymphoma. Throughout the microenvironment, signals are delivered that promote tumor growth. The microenvironment may be amenable to pharmacotherapy because it has common pathways shared among tumors, it is genetically stable, and its resistance is low. The microenvironment has become a primary target in anticancer therapy. Studies with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) have shown that the immunologic signature and the stroma signature affect prognosis, survival, and progression-free survival.[2] Microenvironmental factors have strong prognostic value in many subsets of lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, Hodgkin lymphoma, and chronic lymphocytic leukemia. Angiogenesis has been targeted with agents such as bevacizumab and aflibercept. Bevacizumab, as a single agent and combined with R-CHOP, has been well tolerated in DLBCL and mantle cell lymphoma.[3] R-CHOP plus aflibercept has been associated with high rates of overall response and complete response in patients with DLBCL or follicular lymphoma.[4,5] Lenalidomide is thought to affect several components of the microenvironment, including T cells, natural killer cells, B cells, and angiogenesis[6,7]; it has shown promising activity in mantle cell lymphoma, aggressive non-Hodgkin lymphoma (NHL), NHL, follicular lymphoma, and DLBCL.[8-11] The microenvironment can also be targeted to restore immunosurveillance and break tolerance to tumor antigens. Strategies include the use of monoclonal antibodies, cytokines, immunomodulators, vaccines, and blockade/checkpoints. The extracellular matrix can be targeted with agents such as hedgehog inhibitors, fibroblast growth factor inhibitors, and cytokine inhibitors.

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Controversy: Is Follicular Lymphoma a Curable Lymphoma?

Drs. Bruce D. Cheson and Gilles Salles discussed whether follicular lymphoma (FL) can produce cures in some patients.[1] Dr. Cheson presented evidence that FL is not curable.

FL occurs less often due to lymphoproliferation, but instead to a failure of apoptosis. Yet the drugs used to treat FL were developed to treat proliferating cells. With the availability of monoclonal antibodies and radioimmunotherapy, life expectancy has certainly improved, reaching 91% at 4 years for patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus a monoclonal antibody.[2] An early study showed that rituximab plus CHOP for indolent NHL confers an advantage over CHOP therapy alone.[3] These findings were confirmed in a larger study by the German Low Grade Study Group.[4] A trial of 321 patients with previously untreated, stage III or IV FL randomized patients to receive cyclophosphamide (750 mg/m^2 intravenously, day 1), vincristine (1.4 mg/m^2 intravenously, day 1), and prednisone (40 mg/m^2 orally, days 1–5; CVP) or CVP plus rituximab (375 mg/m^2 intravenously day 1; CVP-R).[5] Patients received 4 cycles of treatment every 3 weeks; those with CR or PR then received another 4 cycles of the same treatment every 3 weeks. The study showed a median OS rate of 83% versus 77% for CVP-R versus CVP, respectively (P=.0290).

A separate study enrolled 201 patients with FL and 90 patients with mantle cell lymphoma (MCL).[6] All patients were previously untreated and had stage III or IV disease. Patients were randomized to receive mitoxantrone (8 mg/m^2, days 3–4), chlorambucil (3 x 3 mg/m^2, days 3–7), and prednisolone 25 mg/m^2 (days 3–7; MCP) with or without rituximab (375 mg/m^2), during a 4-week cycle. After the initial 6 cycles of treatment, patients with a CR or PR received another 2 cycles of the same treatment. Significant differences were seen in both 4-year PFS (71% with rituximab vs 40% without; P<.0001) and 4-year OS (87% with rituximab vs 74% without; P=.0096).

However, in all of the above studies, despite survival improvements, the survival curves fail to reach a plateau, suggesting that patients are continuing to fail, and thus cures are not being obtained. Similarly, the addition of rituximab maintenance in the PRIMA (Primary Rituximab and Maintenance) trial (discussed below) improved PFS, yet the survival curves failed to plateau.[7,8]

A similar observation was made regarding the survival curves from the First-Line Indolent Trial (FIT) trial,[9] which administered a radioactive antibody, and in patients from the FIT trial whose disease changed from Bcl-2–positive to Bcl-2–negative based on polymerase chain reaction analysis.[10]

Treatment with stem cell transplant (SCT) is a risky procedure that includes a low chance of finding a donor match, high procedure-related mortality, high rates of chronic graft versus host disease, and generally reduced quality of life in the relatively few patients who are eligible. New drugs that target the B-cell receptor, phosphatidyl inositol 3-phosphate (PI3K), the mammalian target of rapamycin (mTOR), and other pathways offer exciting options. However, the existence of numerous redundant pathways that control tumor growth, proliferation, survival, and other aspects of tumor cell malignancy makes a cure unlikely, even with emerging compounds. Another challenge to curing FL is that approximately 30% of patients convert from FL to high-grade lymphoma, and their outcome as a group is extremely poor. In summary, Dr. Cheson underscored the failure of PFS curves to show a plateau for limited or advanced disease, thus supporting the conclusion that FL remains incurable.

Dr. Salles presented evidence that FL may be curable. FL is clearly not curable with chemotherapy, nor with bendamustine or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[11-13] OS has notably improved with the addition of rituximab to chemotherapy.[4,15,16] Yet, even after treatment with R-CHOP or R-bendamustine, patients continue to relapse.[17] Therefore, it is necessary to determine how to improve yet again on these treatments.

FL is characterized by slow growth, with little or no proliferation, and the lack of apoptosis. Events such as first progression, second progression, recurrence, and transformation can be traced to long-lived CD20-positive cells self-renewing from the lymphoma stem cells.[18,19] In theory, eradication of these cells could prevent relapse. Treatment options to pursue in the effort to cure FL may include chemotherapy or radioimmunotherapy, new targeted therapies, and immunotherapy. FL is not considered curable with autologous stem cell transplant or radioimmunotherapy, yet some patients may experience a very prolonged PFS after either of these treatments.[20-22] Proteasome inhibitors, Bcl-2 antagonists, and inhibitors of Syk, Btk, mTOR,

and PI3K offer possibilities for the future, but have yet to show any promise of achieving cures in FL. Clearly, few FL patients are candidates for allogeneic SCT; however, PFS curves suggest that cures can be achieved through this procedure.

Durable responses have been achieved after prolonged treatment with rituximab. In the SAKK 35/98 study, 25% of patients who received 8 rituximab infusions were still in remission at 8 years, with a median follow-up of 9.4 years. Treatment consisted of weekly rituximab for 4 cycles followed by 4 cycles of maintenance rituximab every 2 months.[23,24]

The PRIMA trial randomized FL patients to receive R-CHOP followed by either rituximab maintenance therapy or observation.[8] After 3 years of follow-up, no plateau was reached for PFS. However, rituximab maintenance therapy appears to confer an improved PFS (75% with maintenance vs 58% without; $P<.0001$). The 4-year update shows PFS rates of 68% with rituximab maintenance versus 50% without ($P<.0001$). The identical HRs over time suggest stable data. A meta-analysis of rituximab maintenance studies supports the value of this strategy in improving OS in FL patients for relapsed or refractory lymphoma ($P=.005$; HR, 0.72 [95% CI, 0.57–0.91]). However, the data for rituximab maintenance after first-line therapy did not reach significance ($P=.44$; HR, 0.86 [95% CI, 0.60–1.25]).[25] The PRIMA study showed a CR/CRu rate of 72% with maintenance rituximab versus 52% without, 2 years after finishing immunochemotherapy. Thus the quality of initial response predicts OS.[8,26]

The FL2000 study investigated the combination of cyclophosphamide, adriamycin, vindesine, and prednisone (CHVP) plus interferon (CHVP-I), with or without rituximab (CHVP-I-R). The 8-year event-free survival (EFS) with rituximab was 44.1% (95% CI, 36.7–51.7) versus 27.9% (95% CI, 21.1–34.6) without rituximab. The risk of relapse clearly diminishes over time for both treatment groups.

Several studies suggest that the combination of rituximab plus lenalidomide may enhance the effect of immunotherapy by activating killer cells.[27-29] Following on this concept, the phase III RELEVANCE (Rituximab and Lenalidomide versus Any Chemotherapy; FL-001) trial will randomize patients to receive either 1) rituximab plus lenalidomide induction, followed by rituximab plus lenalidomide maintenance or 2) rituximab plus any chemotherapy induction, followed by rituximab maintenance. This international, multicenter, randomized trial will recruit 1,000 treatment-naïve patients for randomization. The next steps are to improve current tools and to continue to develop antibodies, including exploration of bispecific antibodies and antibody drug conjugates. With these tools in hand, it may be possible to cure FL.

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Monoclonal Antibodies Other than CD20 for NHL and HL

Dr. Nancy L. Bartlett discussed monoclonal antibodies, which are being developed not only to bind new targets but also to incorporate new strategies for killing cancer cells.[1] Antibodies that bind directly to tumor cell markers include epratuzumab (CD22), dacetuzumab and lucatumumab (CD40), galiximab (CD80), and blinatumumab (CD19/CD3). Although many of these antibodies are being tested in combination with rituximab, lucatumumab (HCD122) yielded a response rate of 40% in rituximab-refractory patients.[2] Blinatumomab showed intriguing results in a phase I trial of 50 patients, with responses reported in 12 of 12 patients treated at the maximum tolerated dose. Blinatumomab requires a continuous infusion and was associated with dose-limiting neurologic events. Targeting of bystander cells is being investigated as another approach. Two such antibodies have been investigated in phase I trials of lymphoma: ipilimumab—which recently was approved for melanoma—targets CTLA-4,[3] and CT-011 targets PD-1, which regulates apoptosis.[4] In contrast to unmodified antibodies, immunoconjugates may provide anti-cancer activity without the need for an intact immune system. The US Food and Drug Administration recently approved brentuximab vedotin for treating Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL). Inotuzumab ozogamicin is a humanized anti-CD22 antibody conjugated to calicheamicin, a potent cytotoxic antibiotic. Two phase I or II studies suggested good activity in patients with FL.[5,6] Preliminary results from a phase II trial examining inotuzumab ozogamicin combined with rituximab showed very high response rates, including high CR rates, in non-refractory follicular lymphoma and diffuse large B-cell lymphoma.[7] Other immunoconjugates include an anti-tubulin moiety, such as SAR-3419, which binds to CD19 and is conjugated to DM4; and SGN-75, which binds to CD-75 and is conjugated to monomethyl auristatin F.

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Hodgkin Lymphoma in the Elderly: Past, Present, and Future

Dr. Andrew M. Evans discussed HL in the elderly.[1] Elderly patients (those ≥60 years) are under-represented in HL clinical trials, and they lack a standard treatment approach. The rates of EFS and OS are vastly inferior compared to outcomes in younger patients. Reasons for the discrepancy may include comorbidities, inadequate treatment delivery and/or intensity, and treatment-related toxicities, such as bleomycin lung toxicity (BLT). In addition, the disease may differ biologically in older patients and younger patients. Statistics from the Surveillance, Epidemiology and End Results (SEER) database show uneven distribution of HL based on age and race. HL peaks in patients ages 20–29 years, and then again in patients ages 75–84 years. It also peaks in patients ages 60 and older in white patients and, even more markedly, in Hispanic patients. Epstein-Barr virus (EBV) has been associated with HL, but the incidence and prognosis vary according to age. EBV is more common among the youngest patients and the oldest patients. In patients ages 5–14 years, EBV was associated with improved OS and disease-specific survival.[2] In contrast, in older patients (ages 45–96 years), EBV was associated with decreased OS and disease-specific survival.

Prospective studies of HL in the elderly are not abundant; most published studies are retrospective. According to available data, a greater percentage of elderly patients present with advanced disease compared to younger patients. Elderly patients are more likely to have B symptoms and less likely to have bulky disease than younger patients. Mixed cellular histology is more common among elderly patients.[3] Despite its widespread use, the international prognostic scale (IPS)[4] was developed based on data from a patient cohort that included a limited number of older patients (9% of patients were >55 years, and none were >65 years). Therefore, the IPS may not accurately reflect disease in the elderly.

Although OS improved from approximately 20% to approximately 40% between 1980 and 2000 in patients ages 60 years or older, survival in the elderly continues to lag behind all other age groups.[5] Because of the very low OS for patients ages 60 years or older,[6] efforts have been made to improve treatment for this population through decreased intensity of chemotherapy, individualized dosing, reduced dose intensity, and the use of non-anthracycline options. A retrospective analysis of data from 95 elderly patients treated from 2000–2010 showed relatively modest outcomes. The ORR was 85%, with 73% CR. Two-year OS and 5-year OS rates were 73% and 58%, respectively, and 2-year EFS and 4-year EFS rates were 63% and 47%, respectively. Multivariate analysis revealed 2 important prognostic factors: age older than 70 years (HR, 2.24; P=.02), and loss of 1 or more activities of daily living (ADLs) (HR, 2.71; P=.04). None of the IPS factors was identified via multivariate analysis. Lack of CR was the strongest prognostic factor (HR, 8.1; P<.0001). These factors could serve as the basis for developing a new prognostic model for elderly patients with HL.

The E2496 trial enrolled 812 patients, including 43 elderly patients, who were randomized into 2 treatment arms.[7] Patients in arm 1 (n=404) received 6–8 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Modified involved-field radiation therapy (IFRT; 36 Gy) was administered only to patients with massive mediastinal disease. Patients in arm 2 (n=408) received 12 weeks of Stanford V chemotherapy. Modified IFRT (36 Gy) was administered to patients with sites greater than 5 cm in the maximum transverse dimension. The elderly patients had a median age of 65 years (range, 60–83), and 23 patients (54%) were male. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 was recorded for 42 patients (98%), and ECOG PS of 2 was recorded for 1 patient (2%). Forty patients (93%) had stage III or IV disease, and 23 patients (53%) had B symptoms. Analysis of patient and disease characteristics showed several differences for older patients, including worse PS, greater frequency of mixed cellularity, and possibly a reduced frequency of extranodal disease compared to younger patients. The rate of CR plus clinical CR was 65% for the elderly patients, and the ORR was 70%. Analysis of response rate in older versus younger patients showed no significant difference in the rates of CR/clinical CR (P=.49) or ORR (P=.19). Both treatment regimens were toxic to the elderly population. Grade 3/4 non-hematologic adverse events from ABVD treatment occurring in at least 5% of the population included grade 3 fatigue (17%), and 9% of patients experienced grade 3 dehydration, vomiting, hyperglycemia, or myalgia. Of greater concern was the incidence of grade 4 motor neuropathy and sensory neuropathy, which occurred in 9% of patients and is potentially life-threatening. Grade 3/4 non-hematologic adverse events from Stanford V treatment occurring in at least 5% of the population included grade 3 motor neuropathy (15%), and 10% of patients experienced grade 3 muscle weakness,

hyperglycemia, or neutropenic fever. Five percent of patients had grade 3 fever, dysphagia, nausea, or abdominal pain. Five percent of patients had grade 4 constipation or myalgia. Treatment-related mortality was higher in patients older than 60 years versus younger patients (9.3% vs 0.3%; *P*<.001). The overall incidence of BLT was 26%, with an associated fatality rate of 18%. No differences in FFS or OS were detected for the treatment arms (*P*=.80 and *P*=.77, respectively). A significant difference was seen in 3- or 5-year FFS (*P*=.0014) and for 3- or 5-year OS (*P*<.0001) for patients ages 60 years and older versus patients younger than 60 years.

A study by Böll and colleagues examined outcomes from the subset of 117 elderly patients in the HD10 and HD11 studies, and found 67–69% grade 3/4 toxicities, plus a treatment-related mortality of 5%.[8] The analysis again showed outcomes lagging for the elderly: 5-year PFS rate was 79% for elderly patients versus 96% for younger patients in the HD10 trial, and 69% versus 86% in the HD11 trial. The SHIELD (Study for Hodgkin's In the Elderly Lymphoma Database) trial in the United Kingdom is designed to investigate comorbidity, functional scales, and quality of life assessments. The phase II study uses the vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone, and bleomycin (VEPEMB) protocol and has registered 232 patients.

A phase II investigator-initiated, multicenter study is under way in the United States for treatment-naive HD patients ages 60 years or older. The study will investigate treatment with 2 cycles of brentuximab vedotin (SGN-35) at 1.8 mg/kg every 3 weeks. Brentuximab vedotin appears to be associated with comparable rates of severe adverse events in elderly patients versus patients younger than 65 years (*P*=.4013).

HD in the elderly is likely a different disease biologically compared to HD in younger patients. To improve treatment of HD in the elderly, more prospective studies and new therapeutic options are needed. Functional tools such as PET should be examined, and comorbidity and ADL assessments should be incorporated into future studies.

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Mantle Cell Lymphoma—What Is the Current Standard of Care for Older and Younger Patients?

Dr. Brad S. Kahl reviewed the treatment options for patients with MCL.[1] Currently, there is no standard of care for MCL. Aggressive treatment is often used to control the disease, but the disease is not reliably curable. Part of the challenge lies in the fact that MCL is genetically heterogeneous, with variable levels of aggressiveness. Several treatment choices are available and can be broadly classified as less intensive or more intensive.

In MCL patients, R-CHOP produced an ORR of 94–98%, with up to one-half of these patients experiencing a CR.[2,3] PFS ranged from 16–28 months, but it was likely inflated because 14 patients received autologous stem cell transplants (ASCT).

The STiL (Study Group Indolent Lymphomas) trial examined first-line bendamustine plus rituximab (BR) to treat patients with stage III or IV (FL, MCL, or indolent lymphoma.[4] Patients randomized to the test arm (n=260) received bendamustine (90 mg/m^2, days 1 and 2) plus rituximab (375 mg/m^2, day 1) every 4 weeks for a maximum of 6 cycles. Patients in the control arm (n=253) received R-CHOP every 3 weeks for a maximum of 6 cycles. The study population included 93 patients (18%) with MCL, with a median age of 70 years. Forty-five MCL patients received BR, and 48 received R-CHOP. Subanalysis of the MCL population showed that BR was superior to R-CHOP, with a median PFS of 33

months versus 22 months, respectively (*P*=.0146). BR showed a slightly improved toxicity profile, with more erythema (*P*=.0122) and allergic skin reactions (*P*=.003), but reduced parasthesias (*P*<.0001), stomatitis (*P*<.0001), and infectious complications (*P*=.0025). Grade 3 or 4 neutropenia and leukocytopenia were also significantly lower with BR (*P*<.0001 for each). The STiL study suggests that BR efficacy may be at least as good as that of R-CHOP, and BR may cause less overall toxicity. Further studies are needed to extend these early observations.

With MCL, it is relatively easy to establish remission, but it is harder to achieve durable responses. Therefore, it may be feasible to improve response duration through improvements to postremission therapies. A very large randomized clinical trial examined MCL in elderly patients. The trial involved 8 European countries and enrolled 560 patients older than 60 years with performance status of 0–2 and previously untreated stage II–IV MCL. The study involved 2 randomizations. Patients were initially randomized to receive either 8 cycles of R-CHOP or 6 cycles of rituximab, fludarabine, and cyclophosphamide (R-FC). Patients with a response were then randomized to receive maintenance therapy with interferon alfa (IFN-α [3 x 2 M IU weekly], PEG-IFN [1 µg/kg weekly]), or rituximab (every 2 months until disease progression). Based on the maintenance arm treatment alone, remission duration in the intent-to-treat population was improved for patients who received rituximab (median, 77 months) compared to IFN (median, 22 months; *P*=.0004). An analysis of the interaction of induction and maintenance therapies did not reach statistical significance (*P*=.41). Although the patient numbers were relatively low (with 150 patients in the R-CHOP induction arm and 98 patients in the R-FC arm), the analysis of maintenance therapy by induction arm suggested that rituximab maintenance therapy was superior to IFN for patients in the R-CHOP induction arm (*P*=.0005), but no difference was observed for the IFN induction arm (*P*=.11). The study did not reveal any unexpected toxicities for either treatment. Some caution is in order when drawing conclusions from this study. There was significant toxicity from R-FC, and although 560 patients were originally enrolled, only 248 patients were available for the second randomization. The trial was stopped early when an OS benefit was noted for patients in the R-CHOP induction arm. Finally, the study had a complicated design of 2 x 2 factorial.

For patients who can tolerate a more intensive therapy, Dr. Kahl focused on R-CHOP with alternating rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) followed by ASCT. Data from 4 studies that examined intensive treatments produced an estimated ORR of approximately 95% and CR rates of 60–70%.[5-8] Median 5-year, EFS rates ranged from 40% (from an unpublished study with short follow-up) to 65%.

In the MCL Younger Trial, a study by the European MCL Network, patients ages 65 or younger were randomized to 1 of 2 treatment arms. Arm 1 received R-CHOP followed by peripheral blood stem cell transplant (PBSCT), and arm 2 received alternating R-CHOP/R-DHAP followed by PBSCT.[5] The treatments did not yield a difference in OS, but addition of cytarabine appeared to prolong the first remission. After a median follow-up of 32 months, median time to treatment failure (TTF) for the R-DHAP arm was not yet reached, compared to 49 months for the R-CHOP arm (HR 0.68; *P*=.0382). The study suggests that the nature of the induction therapies administered prior to ASCT may have an impact on PFS.

Several reasonable intensive treatment strategies are available, and no single standard of care has been established to date. For patients with MCL, a clinical trial is usually the best treatment option. Future clinical trials should eventually lead to a standard of care to which future regimens can be compared.

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Novel Agents With Activity in CLL/SLL

Dr. Susan O'Brien discussed results from early-phase clinical trials of 3 orally available inhibitors of the B-cell receptor (BCR) pathway in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).[1] The agents include the spleen tyrosine kinase (Syk) inhibitor fostamatinib, the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765, and the phosphatase inositol 3 kinase delta (PI3Kδ) inhibitor CAL-101.

Fostamatinib disodium is a small-molecule inhibitor of Syk. Its safety has been demonstrated in healthy human subjects. A phase II study examined the inhibition of Syk with fostamatinib disodium in non-Hodgkin lymphoma (NHL) and CLL.[2] Eleven patients in the study had CLL/SLL. The drug was orally administered at 200 mg twice daily. Two patients had stable disease. Hypertension of any grade was observed in 20% of patients. Grade 3/4 hematologic toxicities included neutropenia (17%, including 7.5% with febrile neutropenia), anemia (7%), increased aspartate aminotransferase (4%), and thrombocytopenia (3%). Fostamatinib yielded an ORR of 55%, based on 6 of 11 CLL/SLL patients with a PR using standard lymphoma response criteria (ie, without considering the patient's white blood cell count). Fostamatinib is currently under investigation in rheumatoid arthritis but not in lymphoma.[3]

PCI-32765 inhibits Btk, a component of the BCR signaling pathway that acts downstream of Syk. Administered orally, it forms a specific and irreversible bond to Btk, and it has a half maximal inhibitory concentration (IC_{50}) of 0.5 nM. Daily dosing results in 24-hour target inhibition. In CLL cells in vitro, PCI-32765 promotes apoptosis and inhibits CLL cell migration and adhesion, as well as CpG-mediated proliferation.[4-6] Interim results were reported for a phase Ib/II study that examined PCI-32765 activity in 3 cohorts. Cohort 1 included treatment-naïve patients older than 65 years. Cohort 2 patients had relapsed or refractory disease and had received at least 2 prior regimens, including a purine analog. For these 2 cohorts, an absolute neutrophil count (ANC) of at least 0.75 x 10^9/L and a platelet count of at least 50 x 10^9/L were required. In light of the lack of myelosuppression seen with the drug, a third cohort was added to examine patients with relapsed or refractory disease, but without the requirement for ANC and platelet counts. The dose was 420 mg/day for cohorts 1 and 2 and 840 mg/day for cohort 3. Patients in the relapsed or refractory groups had received a median of 3 prior treatments (range, 2–10) for cohort 2 and a median of 5 prior treatments (range, 2–12) for cohort 3. Information on prognostic markers, including 17p deletion, 11q deletion, and immunoglobulin heavy chain variable region (IgVH) mutation, was available for a subset of patients in each cohort. To date, only 3 patients have been removed from the study due to disease progression, all in the relapsed/refractory cohorts. Two deaths have occurred, both in the 840 mg/day relapsed/refractory cohort. Myelosuppression is a major complication of chemotherapy in CLL patients. In contrast, a notable finding from the current study was the very low rates of myelosuppression. The most common adverse event of any grade was diarrhea, which occurred in 48% of the treatment-naïve patients and 70% of the relapsed/refractory patients. Other adverse events of any grade occurring in at least 30% of patients included nausea (39%) in the treatment-naïve cohort, and upper respiratory infection (37%), fatigue (33%), nausea (33%), and contusion (33%) in the 420 mg/day cohort. No grade 4 adverse events were reported.

An important aspect of the response to treatment with PCI-32765 is the lymph node shrinkage without a concomitant decrease in the white blood cell count. To describe the novel response pattern observed with these new drugs, the authors have defined a "nodal response" as lymph node shrinkage of at least 50% in the absence of a 50% or greater reduction in the lymphocyte count. The treatment-naïve cohort showed a response rate of 67%, comprising 1 CR (5%) plus 15 PRs (62%). The response rate was based on the standard response criteria that includes a 50% reduction in white blood cell count. In addition, 4 patients (19%) showed a nodal response, as defined above. In the relapsed/refractory cohort that received 420 mg/day, an ORR of 48% was observed, including 1 (4%) CR and 12 (44%) PRs. Eleven patients (41%) had a nodal response. In total, 42 of 48 patients (88%) in cohorts 1 and 2 experienced nodal shrinkage.

Dr. O'Brien noted that patients who initially exhibit a nodal response may convert to a PR over time because the reduction in white blood cell counts often occurs later with this drug. Thus, the time point for patient evaluation is important. Patient response did not appear to depend on the prognostic factors of 17q deletion, 11q deletion, or IgVH mutation. Some patients showed a dramatic improvement in platelet count.

PI3Kδ mediates the intracellular signaling induced by several extracellular receptors, including the BCR. CAL-101 is an oral agent that binds specifically to the delta isoform of PI3K, with an EC50 of 8 nM. Following an earlier phase I trial, which explored CAL-101 doses ranging from 50 mg twice daily to 350 mg twice daily, plus CAL-101 150 mg/day or 300 mg/day, a phase I trial was undertaken to examine clinical activity and pharmacodynamic effects in CLL patients. The trial enrolled 55

patients (82% male) with relapsed or refractory CLL and a median age of 63 years (range, 37–82).[7] The patients had received a median of 5 prior therapies (range, 2–15). The adverse prognostic factor of 17p deletion was observed in 31% of patients. Four patients in the intent-to-treat (ITT) population were removed from the study early. Tumor shrinkage was observed in all of the remaining 51 evaluable patients, including all of the patients with 17p deletion. The trial showed an ORR of 24%. However, the nodal response rate was 84%. At the same time, treatment with CAL-101 improved the mean platelet counts and mean hemoglobin values. CAL-101 was well tolerated in patients with CLL, even over exposure periods greater than 1 year. Transaminase elevations may occur but may be self-limited or may resolve with treatment interruption, which can be followed by resumption of treatment at a lower dose. A phase II trial currently under way will evaluate CAL-101 in combination with rituximab in treatment-naïve elderly patients with CLL/SLL. Patients (N=60) will receive weekly infusions of rituximab (375 mg/m^2) for 8 weeks plus CAL-101 (150 mg) orally twice daily until disease progression or unacceptable toxicity.[8]

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Novel Agents for Targeting the B-Cell Receptor, Signal Transduction, and Kinase Pathways

Dr. Thomas E. Witzig reviewed drugs that attack molecules associated with a variety of intracellular pathways, including the B-cell receptor (BCR), CD22, Syk, Bruton's tyrosine kinase (Btk), protein kinase C, farnesyl transferases, PI3K, and the mammalian target of rapamycin (mTOR).[1] Epratuzumab is a monoclonal antibody that binds to CD22, which increases the receptor's ability to inhibit B-cell activation. In a phase II trial, patients with previously untreated diffuse large cell B-cell lymphoma (DLBCL) received standard rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP) therapy plus epratuzumab (360 mg/m^2 intravenously) over 60 minutes on day 1 of the treatment cycle. The combination therapy was well tolerated, and preliminary results showed improved outcomes compared to studies of R-CHOP alone.[2] Syk and Btk are 2 molecules downstream of the BCR that are targeted by fostamatinib and PCI-32765, respectively. Both fostamatinib and PCI-32765 are fairly well tolerated and have yielded best response rates of 50% ORR and 69% ORR in chronic lymphocytic leukemia/lymphoma and small lymphocytic leukemia, respectively.[3] Results from a phase II trial of tipifarnib, a farnesyl transferase inhibitor, showed a somewhat low ORR of 20% (19 of 93 patients). However, patients with DLBCL experienced a median duration of response of 11.3 months (range, 4.9–17.1 months). Tipifarnib also showed activity in patients with Hodgkin lymphoma and T-cell lymphoma.[4] Dr. Witzig also reviewed findings on CAL-101, which targets PI3Kδ, and everolimus and temsirolimus, which target mTOR. CAL-101 monotherapy has shown very promising activity—including some evidence of durable response—in chronic lymphocytic leukemia/lymphoma, indolent lymphoma, and mantle cell lymphoma in early trials. Both everolimus and temsirolimus have continued to show encouraging results in phase I and II trials, warranting their continued study. Accordingly, a large international study is under way examining everolimus as consolidation therapy after R-CHOP. The mTORC1 and mTORC2 complexes represent 2 separate pathways, and drugs that target both pathways are in the pipeline.

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Peripheral T-Cell Lymphoma (PTCL)—Update on Novel Therapies

Dr. Julie M. Vose discussed novel therapies in PTCL, a group of aggressive mature T-cell and natural killer (NK) cell lymphomas.[1] PTCL refers to the involvement of more mature, post-thymic T-cells, as compared to less mature, pre-thymic T-cells.[2] Examination of OS in PTCL patients according to subgroups shows that, for most PTCL patients, standard therapies are not very effective, with 5-year OS ranging from 14% for adult T-cell leukemia/lymphoma (ATLL) to 70% for ALK-positive anaplastic large cell lymphoma (ALCL).[3] A new prognostic index for PTCL (PIT) has been developed to address limitations of the older IPI.[4,5] The PIT predicts outcome based on the number of risk factors, and it appears to be more accurate than the IPI used for NHL.

Standard therapies for aggressive B-cell lymphomas do not work well for PTCL, and there continues to be a need for effective salvage therapy. Stem cell transplant is valuable for some patients, but there is still a need to better define when this option is appropriate. New agents represent the best option for improving treatment for PTCL, and among those in development are chemotherapies, HDAC inhibitors, and kinase inhibitors. Other therapies are in development to specifically target T-cell surface antigens and receptors, inhibit cell survival mechanisms, and target microenvironmental factors, such as angiogenesis.

Pralatrexate is a selective antifolate rationally designed to accumulate in cancer cells that express RFC-1. Intracellular polyglutamylation promotes intracellular retention of the drug. By interfering with DNA synthesis, pralatrexate induces cancer cell death.[6-8] The PROPEL (Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma) study was a pivotal phase II, nonrandomized, open-label, international study of pralatrexate in patients with relapsed or refractory PTCL.[9] Based on the PROPEL study, pralatrexate became the first agent approved for treating PTCL. Pralatrexate (30 mg/m^2) was given intravenously weekly for 6 weeks out of a 7-week cycle, with supplementary vitamin B_{12} (1 mg intramuscularly over 8–10 weeks) and folic acid (1.0–1.25 mg orally daily), until disease progression or treatment intolerance. Dr. Vose noted the importance of giving vitamin B_{12} and folic acid at least 10 days before starting pralatrexate treatment, in order to prevent mucositis. A decrease in tumor size was observed in 75% of patients with measurable disease. The mean duration of treatment for all treated patients was 112 days (range, 1–558 days). For responders, per the International Workshop Criteria (IWC), the median duration of response was 234 days (range, 1–558 days), with durable responses observed for some patients. Adverse events were manageable and were consistent with those seen for other drugs of the antifolate class. The most common grade 3/4 nonhematologic toxicity was mucositis, which occurred in 24 patients (22%). Other grade 3/4 toxicities included dyspnea and fatigue, each observed in 8 patients (7%). The ORR was 28%. Median OS was 14.7 months, and median duration of response was 9.4 months. (Updated results, presented in 2011, were similar. The ORR was 29%, including 12 patients [11%] with a CR or CRu, and 20 patients [18%] with a PR. The median duration of response was 10.1 months, and median OS was 14.5 months.[10])

Other agents showing promise in the treatment of PTCL include bendamustine, etoposide, and romidepsin. Romidepsin is a novel, potent, bicyclic HDAC inhibitor. It was approved by the US Food and Drug Administration (FDA) in 2009 for patients with mycosis fungoides and, more recently, for PTCL. Activity in PTCL patients has been observed in phase I and phase II trials.[11,12] In addition to HDAC inhibition, romidepsin appears to disrupt angiogenesis and the cell cycle.[13] A phase II, open-label, single- arm, international study investigated romidepsin in 130 patients with histologically confirmed, relapsed or refractory PTCL. Patients had failed at least 1 prior therapy and had measurable disease by IWC and/or measurable cutaneous disease. Romidepsin was given as a 4-hour infusion (14 mg/m^2) on days 1, 8, and 15 in a 28-day cycle. The ORR (CR plus CRu plus PR) was 26% (34 patients), which 13% CR/CRu (17 patients). Durable responses were observed in some patients. The most common adverse events of any grade were nausea, infection, and fatigue. The most common grade 3/4 treatment-emergent adverse events were grade 3 thrombocytopenia, neutropenia, and infection. Other HDAC inhibitors are also under investigation for PTCL.

Dasatinib is a multikinase inhibitor that binds to BCR-ABL, Src, c-kit, and PDGFR tyrosine kinases.[14,15] It was recently approved as first-line therapy for chronic-phase chronic myelogenous leukemia. Syk, which acts downstream of BCR, is overexpressed in many PTCL patients, including 100% of patients with angioimmunoblastic lymphoma, and 64% of patients with PTCL NOS.[16] A phase I/II dose-escalation study examined 3 cohorts of PTCL patients with relapsed or refractory NHL. Dasatinib

was administered daily at 100 mg, 150 mg, or 200 mg. Out of 19 patients, 2 CRs were observed in PTCL patients, and the duration of response currently for these patients is over 3 years, with the patients receiving continuous low-dose dasatinib. Another PTCL patient experienced a PR.

Translocations of the JAK2 locus on chromosome 9 may be of oncogenic importance in PTCL.[17] Thus, the JAK-STAT pathway presents another area to target for patients with PTCL. Inhibitors of the JAK-STAT pathway that may be of interest for treating PTCL include cucurmin, flavopiridol, resveratrol (SRT501), stiprimod, CDDO-Me (RTA402), and OPD-31121. Other agents of interest in treating PTCL include lenalidomide and brentuximab vedotin, which showed activity in relapsed or refractory T-cell lymphoma and systemic ALCL, respectively. Brentuximab vedotin is an anti-CD30 monoclonal antibody conjugated to an antitubulin molecule, monomethyl auristatin E, with a protease-cleavable linker that allows release of the tubulin inhibitor. In a phase II study in 58 patients with relapsed or refractory ALCL, brentuximab vedotin was administered intravenously at 1.8 mg/kg every 28 days. Reduced tumor size was reported in 57 of 58 patients (97%). Among 57 evaluable patients, 31 CRs (54%) and 19 PRs (33%) were observed. The median PFS has not yet been reached for patients with CR, and it was 19 weeks for patients with PR. Continued investigation of new drugs, as well as new combinations, and the inclusion of gene expression profiling to enable effective patient selection will be important for discovering the optimal therapies for treating PTCL.

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Inducing Apoptosis in Lymphoma Cells Through Novel Agents

Dr. Owen A. O'Connor examined the use of novel agents to induce apoptosis in lymphoma cells.[1] In contrast to normal cells, cancer cells have mechanisms allowing escape from the induction of apoptosis from stresses such as hypoxia, abnormal cell cycle progression, and chemotherapy exposure. The complexity of the apoptosis machinery provides numerous components for building effective antitumor strategies. The family of Bcl-2 proteins governs apoptosis and is critical in several different lymphomas, as well as other cancers. Apoptosis occurs through 1 of 2 pathways: the extrinsic pathway, which is stimulated by external factors, and the intrinsic pathway, which is mediated largely through changes in cell membrane composition and through regulatory proteins in the mitochondrial cell membrane. The TNF-related apoptosis-inducing ligands (TRAIL) receptor family stimulates the extrinsic apoptosis pathway.[2] Efforts to modulate TRAIL include use of antibodies, small molecules, peptides, and the ligands themselves.

Mapatumumab is an agonistic antibody that binds to the TRAIL-R1 receptor (also known as DR4) and activates caspase. A phase Ib/II trial tested mapatumumab in patients with relapsed or refractory NHL.[3] No dose-limiting toxicities (DLTs) were noted. Out of 40 patients, 17 had FL; 3 responses were observed in FL patients. Although the target seems rational, the modest response rate suggests that the approach needs refinement.

The intrinsic pathway has garnered more attention recently as an alternative strategy for inducing apoptosis in cancer cells. Disrupting the intrinsic machinery is challenging, however, due to the large number of regulatory proteins involved. The Bcl-2 family contains more than a dozen genetically related molecules, including Bcl-2 itself. The family contains both pro- and anti-apoptotic proteins, plus BH3-only mimetics. BH3 is a binding domain that mediates binding of the different family members and therefore represents a target that may be amenable to pharmacotherapy. Binding via the BH3 domain liberates the pro-apoptotic proteins Bak and Bax.[4]

Oblimersen sodium is an 18-nucleotide oligomer that selectively targets Bcl-2 RNA, leading to reduced levels of the Bcl-2 protein.[5] The drug was tested in combination with fludarabine and cyclophosphamide in a phase III trial of CLL patients, but it did not receive FDA approval because the magnitude of the difference obtained by adding oblimersen was deemed too small. Navitoclax/ABT-263 is an orally available BH3 mimetic. In a phase I/IIa study of patients with relapsed or refractory lymphoid malignancies, it showed promising activity in patients with CLL.[6] GOSSYPOL/AT-101 is a polyphenolic aldehyde from the cottonseed plant genus *Gossypium*. It binds with high affinity to the BH3 binding pocket of BHL-xL. Its pro-apoptotic ability lies partly in its ability to upregulate Noxa and Puma, 2 pro-apoptotic Bcl-2 family members. In a phase II study of 23 patients with untreated FL, for the induction phase, AT-101 (30 mg orally) was administered daily for 21 days in combination with rituximab (375 mg/m^2) weekly for 4 weeks. Maintenance treatment was AT-101 (30 mg) orally for 21 days plus rituximab (375 mg/m^2) every 8 weeks. The median age was 64 years. Sixty-one percent of patients had stage IV disease, and 35% had bulky disease. After induction, the study showed an ORR of 26%, including 4% CR; overall, the study showed 70% ORR, including 35% CR. The impact of AT-101 is difficult to discern without a control arm.[7]

Obatoclax is the third anti-BH3 small molecule in clinical trials. It inhibits Mcl-1 in addition to BCL-xL, Bcl2, and BCLW. In a phase I trial, obatoclax was administered via 3-hour infusion every 3 weeks. The MTD was 28 mg/m^2 every 3 weeks. Out of 26 enrolled patients, 1 PR was observed at 3.5 mg/m^2, and 2 patients became transfusion-independent. At all doses, sustained improvements in platelet and hemoglobin levels were seen (4 of 14 and 3 of 11 patients, respectively).[8]

The inhibitors of apoptosis (IAPs) govern the half-life of NF-κB. Alterations in IAPs are prevalent in many types of cancer and are associated with chemoresistance and poor prognosis. Small-molecule IAP antagonists are also known as Smac mimetics. They cause rapid depletion of cellular IAPs, thus allowing apoptosis to ensue. At least 5 different IAP inhibitors are in early-phase clinical development. In order to develop effective therapeutics, it is important to consider not only the presence of Bcl-2, but also the presence of activator molecules. These may be triggered by malignant features such as genomic instability, oncogene activation, and the eradication of cell cycle checkpoints. A therapeutic window has been proposed that may allow the targeting of Bcl-2 and its associated molecules in cancer cells, which generally contain primed Bcl-2 molecules, while sparing normal cells, in which Bcl-2 occupation by activators is less common.[9] Although the agents that target the apoptosis pathway have shown modest single-agent activity, they could be effective in combination with other agents. For example, ABT-737 is a BH3-mimetic that has been combined with bortezomib, a proteasome inhibitor, with evidence of synergistic activity in vitro against a panel of MCL and DLBCL cell lines.[10] Anti-apoptotic compounds have the potential to grow into a new class of viable therapeutic anticancer agents. The most likely setting for these new agents may be in combination with other agents. Simultaneous targeting of the same pathway is a strategy worth considering. Anti-apoptotic agents must be developed with knowledge of how growth and survival pathways interact with the apoptotic machinery.

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Commentary

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A number of important themes emerged at the Pan Pacific Lymphoma Conference, which included seminars, debate-type presentations, clinical case conferences, and symposia. Perhaps some of the more interesting discussions focused on novel agents for the treatment of lymphomas.

For at least the more indolent lymphomas, the goal of treatment is to move away from chemotherapy to more targeted therapeutics. Some of those agents—notably, monoclonal antibodies—are directed at the cell surface, others are involved in inhibiting intracellular pathways, and some affect the microenvironment. Monoclonal antibody therapies, such as rituximab, have clearly revolutionized the treatment of lymphomas and have improved the survival of patients with indolent and aggressive forms of the disease. However, we are now moving far beyond the standard monoclonal antibody. At the Pan Pacific Lymphoma Conference, presentations included updates of the drug antibody conjugates, a class of agents in which a monoclonal antibody is linked to a toxin. The antibody binds specifically to the tumor cell and is internalized, whereupon the toxin is released and kills the tumor cell. Recently, the US Food and Drug Administration (FDA) approved one such drug, brentuximab vedotin, also known as Adcetris. This drug was shown to be exquisitely active in patients with relapsed and refractory anaplastic large-cell lymphoma, an aggressive form of T-cell lymphoma, with a response rate of about 86%, including more than 50% complete remissions—results unheard of up to this time.[1] Brentuximab vedotin was also shown to be quite active in Hodgkin lymphoma, with response rates of approximately 75%, which included a complete remission rate of about one third, in patients who had failed a prior stem cell transplant.[2] Studies are in development to move this agent earlier in the course of the disease, even to frontline therapy. Not only are these results extremely exciting by themselves, but they provide a foundation for further study of this novel class of agents. Indeed, there are now several drug antibody conjugates for other forms of lymphoma in phase I, II, and III testing.

Regarding the intracellular pathways, activation of the B-cell receptor is important for the perpetuation of the malignant lymphocyte through downstream signaling pathways, such as those involving the PI3 kinase and Bruton's tyrosine kinase (Btk). Drugs in development include CAL-101, which inhibits a specific isoform of the PI3 kinase pathway,[3] and PCI32765, which is a specific inhibitor of the Btk pathway.[4] Both of these agents have shown impressive activity, with exceptional tolerance, in the setting of a spectrum of histologies of B-cell malignancies. These drugs are oral and well tolerated, and they are now being combined with other more traditional agents, giving us great optimism for newer, more active treatments in the future.

Other intracellular pathways of importance are those that lead to apoptosis or programmed cell death. We now have a number of novel compounds that affect either the intrinsic or extrinsic apoptotic pathways. Apoptosis is defective in patients with B-cell malignancies, and by reactivating programmed cell death, these agents may affect cell kill.

A number of studies have clearly demonstrated the importance of the microenvironment in the malignant process. Lenalidomide purportedly acts on the microenvironment, although its exact mechanisms of action are uncertain. This second-generation immunomodulatory agent has been shown to be active in a variety of histologies of B- and T-cell lymphomas, including Hodgkin lymphoma and mantle cell lymphoma, in which a 50% response rate has been reported in patients with relapsed/refractory disease.[5] These observations have led to further study of this agent in combination with more traditional drugs, such as bendamustine, as the initial treatment for patients with mantle cell lymphoma. All of these drugs are also active in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, as was discussed at the Pan Pacific Lymphoma Conference.[6]

One particularly interesting controversy debated at the conference was whether follicular lymphoma is a curable disease.[7] It is only since the availability of rituximab that we have improved the survival of these patients. Regardless of which chemotherapy regimen the antibody is combined

with, overall response rates, complete remission rates, progression-free survival, and overall survival have been improved. Nevertheless, the question remains as to whether follicular lymphoma is curable, or whether it should now be considered more of a chronic disease. In this debate, the conclusion was relatively clear that even limited-stage patients or those treated with stem cell transplant may have prolonged disease-free survival, but cure in a substantial number of patients remains to be demonstrated.

Finally, the issue of risk-adapted therapy was discussed.[8] There is an increasing body of data examining whether technology such as positron-emission tomography (PET) scanning can be used to direct therapy in patients with malignant lymphoma. The goal would be to identify patients at poor risk with standard treatments, who could then move on to alternative approaches (such as dose intensification), and patients at low risk, to determine whether limiting the amount of treatment could provide effective results with reduced toxicity. Although the great weight of evidence suggests that interim PET scanning is not clinically useful in patients with diffuse large B-cell lymphoma, it appears that it may be valuable in patients with advanced Hodgkin lymphoma. There are now numerous studies around the globe testing this concept in a prospective manner. For example, the Cancer and Leukemia Group B (CALGB) Action Group has one study for patients with limited-stage disease and another study for patients with limited-stage bulky disease. The North American Intergroup has a study for patients with advanced-stage Hodgkin lymphoma.

A previously neglected group of patients have been those with peripheral T-cell lymphoma. At the Pan Pacific Lymphoma Conference, presentations provided a new menu of active drugs, biologics, and antibodies that now provide hope for patients with these lymphomas, which previously had carried a dismal prognosis.[9]

Summary

The Pan Pacific Lymphoma Conference provided an outstanding review of the biology of lymphomas, standard treatment approaches, and novel therapeutics, which might alter our paradigms in the future. New ways of assessing patient outcome may lead to additional clinical benefit.

Acknowledgment

Dr. Cheson is a consultant for Cephalon.

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