Meeting Highlights

Chemotherapy Foundation Symposium XXIV: Innovative Cancer Therapy for Tomorrow

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The goals of the 24th annual Chemotherapy Foundation Symposium, which took place in New York City from November 8 to 11, 2006, were to relate the extensive scope and intensive coverage of emerging advances in the treatment of various neoplastic diseases to an audience of approximately 1,600 oncologists, hematologists, radiotherapists, immunologists, pharmacists, and other allied cancer professionals. The following summary covers some of the important presentations on hematological malignancies.

Clofarabine in Adult Acute Myelogenous Leukemia

Presenter: Stefan Faderl, MD, Associate Professor, University of Texas MD Anderson Cancer Center, Houston, Texas

The standard therapy for acute myelogenous leukemia (AML) continues to be based on cytarabine (ara-C, DepoCyt, Enzon), typically in combination with anthracyclines such as idarubicin (Idamycin, Pfizer) or daunorubicin (Cerubidine, Bedford). Although 60% to 70% of patients achieve complete remissions (CRs), most patients relapse and ultimately die of the disease or of associated complications. This is particularly true for patients older than 60 years of age.

Clofarabine (Clolar, Genzyme) is a next-generation nucleoside analogue, developed as a rational extension of the experience with fludarabine phosphate (Fludara, Berlex) and cladribine (Leustatin, Ortho Biotech). Clofarabine has a high affinity for the enzyme deoxycytidine kinase, the rate-limiting step in nucleoside phosphorylation. It is retained longer within the cells than other compounds in the same class. Although it has been approved by the Food and Drug Administration (FDA) for the treatment of pediatric relapsed or refractory acute lymphoblastic leukemia (ALL), the focus has shifted to AML in adults.

Clofarabine has shown single-agent activity in AML in a phase 2 study that included 39 patients with relapsed and refractory AML and myelodysplastic syndromes (MDS). The clofarabine dose was 40 mg/m² IV daily for five days every three to six weeks. Of the 39 AML patients, 13 (42%) achieved CRs.

In a different study of clofarabine plus cytarabine in patients with relapsed or refractory AML and high-risk MDS, clofarabine was administered as a one-hour IV infusion for five days, followed four hours later by cytarabine 1 g/m² per day as a two-hour IV infusion for five days. Of the 29 patients with AML and high-risk MDS, seven (24%) achieved CRs and five (17%) achieved partial remissions (PRs). The overall response rate was 41%.

In another study of patients older than 50 years of age, a clofarabine/cytarabine combination produced an overall response rate of 60%. Toxicities were manageable, and the mortality rate after chemotherapy induction was low (below 10%).

Clofarabine can be used either alone or in combination with other agents. Combinations with cytarabine in particular appear to be safe and effective. Clofarabine is especially appealing for the treatment of older individuals with AML who are considered to be either unsuitable for standard therapy or unlikely to benefit from it.

Treatment Strategies for Acute Myeloid Leukemia and Myelodysplastic Syndromes in the Elderly Population

Presenter: Gail Roboz, MD, Associate Director, Leukemia Program, Assistant Professor of Medicine, Weill Medical College of Cornell University, New York

The prognosis of AML and advanced MDS in elderly patients is extremely poor. Conventional chemotherapy strategies carry high rates of morbidity and mortality upon induction; they offer only a slight chance of long-term success and should therefore be avoided. However, low-dose cytarabine (ara-C) in combination with other agents, such as arsenic trioxide or gemtuzumab ozogamycin (Mylotarg, Wyeth), in patients older than 60 years of age significantly improves overall survival.

The farnesyltransferase inhibitor tipifarnib (R115 777, Johnson & Johnson), when administered at 600 mg orally twice daily for 21 days, is under investigation for patients 65 years of age and older with high-risk AML and MDS. An ongoing phase 2 study of AML and MDS in elderly patients is using gemtuzumab in combination with low-dose cytarabine and non-myeloablative stem-cell transplantation.

Survival and low toxicity in elderly patients are the key endpoints in these trials. The results are expected at the end of the year.

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Azacytidine plus Thalidomide in Myelodysplastic Syndromes and Acute Myelogenous Leukemia

Presenter: Azra Raza, MD, Professor of Medicine, and Chief of Hematology Oncology University of Massachusetts, Worcester, Massachusetts

The DNA methyltransferase inhibitor 5-azacytidine (Vidaza, Pharmion) elicits complete and partial hematological responses in about 50% of patients with MDS, improves quality of life, and prolongs the time to AML transformation, compared with supportive care. Thalidomide has produced a 20% improvement in MDS patients.

A study used low-dose 5-azacytidine (75 mg/kg) subcutaneously every four weeks and thalidomide 50 mg/day, increased to 100 mg/day. Therapy in 29 patients (median age, 70 years) was continued until disease progression or for one year. Therapy was well tolerated. Fourteen patients responded, and 43% experienced CRs. Thus, it appears that a lower-dose combination of 5-azacytidine and thalidomide might benefit both MDS and AML patients.

Pixantrone: An Anthracycline Derivative for Non-Hodgkin’s Lymphoma

Presenter: John P. Leonard, MD, Clinical Director, Center for Lymphoma and Myeloma, and Associate Professor of Medicine, Weill Medical College of Cornell University and New York–Presbyterian Hospital, New York

Anthracyclines and their derivatives are an integral part of the management of many patients with non-Hodgkin’s lymphoma (NHL). Cardiac toxicity is a major side effect of these agents. The search for an agent with less cardiotoxicity and improved therapeutic activity has resulted in the discovery of pixantrone, an aza-anthracenedione similar in structure to doxorubicin, thereby providing improved therapeutic activity with a lower risk of cardiotoxicity. Pixantrone is currently under development as a single agent, as well as in combination with other agents.

Pixantrone is an anthracycline derivative that is currently under evaluation in clinical trials. It is a novel agent that has demonstrated significant antileukemic activity in vitro and in vivo.

In a phase 2 study, 33 patients (median age, 66 years) with relapsed aggressive lymphoma (diffuse large B-cell lymphoma or mantle-cell lymphoma) were given pixantrone 85 mg/m² on day 1 and then 40 mg/m² on day 29 of each cycle. The principal toxicity was neutropenia. Five complete responses and four partial responses were noted and were associated with the time to disease progression of up to more than 17 months.

These encouraging single-agent data led to additional studies of pixantrone in combination with, or as a substituting agent in, a number of standard lymphoma regimens. These include substitution for the following agents:

- doxorubicin in the CHOP regimen: cyclophosphamide (Cytoxan, Bristol-Myers Squibb), doxorubicin (Adriamycin, Bedford), vincristine (Oncovin, Eli Lilly/Gensia Siroc), and prednisone
- mitoxantrone (Novantrone, Serono/OSI Oncology) in the FND-R regimen: mitoxantrone, fludarabine, dexamethasone, and rituximab (Rituxan, Genentech)
- etopoide (Vepesid, Bristol-Myers Squibb) in the ESHAP regimen: etopoide, methylprednisolone (Solu-Medrol, Pfizer), high-dose cytarabine, and cisplatin (Platinol, Bristol-Myers Squibb)

All of these novel combinations have demonstrated acceptable toxicity and have been encouraging as a result of their efficacy.

In a study published in 2006, 32 patients with relapsed indolent NHL were randomly selected to receive rituximab (Rituxan) or rituximab plus pixantrone. More than a doubling of the response rate with the pixantrone/rituximab regimen was observed (75% vs. 33% with rituximab alone). The time to progression (13.2 months vs. 8.1 months with rituximab alone) was also improved, but this therapy was also associated with more serious adverse effects that were related to cytopenia.

In all of the studies (a total of 271 patients), there was a 13% decline in ejection fraction (grade 1 or 2), and heart failure was low (3%) in all patients, eliciting a good cardiac profile.

These are encouraging results. Additional studies are planned to show the usefulness of pixantrone combined with standard regimens for treating lymphoma. Pixantrone can be used in patients who have already received anthracyclines. Trials are ongoing to determine whether pixantrone can be substituted for doxorubicin in patients with aggressive large-cell lymphoma.

Obatoclax for Chronic Lymphocytic Leukemia: A Clinical Phase 1 Study

Presenter: Susan O’Brien, MD, Professor, Department of Cancer Medicine, University of Texas MD Anderson Cancer Center, Houston, Texas

Obatoclax (GX15-070, Gemin X Biotechnologies) was designed to restore apoptosis, the natural process of cell death that is often inhibited in cancer cells. Overexpression of the Bcl-2 family protein inhibits apoptosis and has been observed in a wide range of cancers, including those of the lymph, breast, lung, prostate, and colon.

Obatoclax inhibit all of the anti-apoptotic members of the Bcl-2 protein family, thus inducing apoptosis in cancer cells without damaging normal cells. It is the first such small-molecule, pan-inhibitor of Bcl-2 proteins tested in clinical trials. It inhibits the binding of the anti-apoptotic proteins Bcl-2, Bcl-xl, Bcl-w, and Mcl-1 to the pro-apoptotic proteins Bax and Bak. It shows broad single-agent cytotoxicity in cancer cell lines in vitro and in vivo. Bcl-2 family proteins are overexpressed in chronic lymphocytic leukemia (CLL), in which accumulation of malignant cells is thought to be the direct result of the consequent inability to undergo apoptosis. Obatoclax was shown to induce apoptosis in human B-CLL cells in vivo.

Obatoclax has shown biological and clinical activity as a single agent in patients with refractory lymphomas and several types of leukemia. Primary side effects are infusion-related somnolence; euphoria; and immunosuppression, organ damage, or cumulative toxicities with no significant myelosuppression.

Three phase 1 clinical trials were conducted to evaluate obatoclax as a single agent in patients with CLL, refractory solid tumors or lymphomas, MDS, or AML. A variety of dosing schedules ranged from 1- to 24-hour infusions, given weekly to every three weeks. A weekly 24-hour infusion
seemed to give the best results. Biological activity was confirmed by direct, dose-dependent activation of Bax and Bak. In addition, clinical activity was shown by partial responses in CLL and follicular lymphomas, prolonged disease stabilization in large-cell lymphoma, and hematological responses, resulting in both red blood cell and platelet transfusion independence (without the need for blood products). Phase 2 studies of obatoclax as a single agent started in the third quarter of 2006; combination phase 1 and 2 studies were planned for the fourth quarter of this year.

**New Tyrosine Kinase Inhibitors for Chronic Myelogenous Leukemia**

**Presenter:** Hagop Kantarjian, MD, Chairman and Professor, Leukemia Department, University of Texas MD Anderson Cancer Center, Houston, Texas

Nearly 70% of patients with early-chronic-phase CML who receive imatinib mesylate (Gleevec, Novartis) achieve a complete cytogenetic response. After a median follow-up of five years, the annual rate of resistance with progression was 4%, and the annual mortality rate was 12%.

In 30% to 50% of cases, resistance to imatinib occurs because of point mutations in the kinase domain of Bcr-Abl. Other mechanisms of resistance include Bcr-Abl-dependent overexpression and amplification and Bcr-Abl-independent mechanisms (overexpression of Src family–related kinases). Thus, there is interest in developing new agents to overcome or prevent the development of resistance to therapy.

**Dasatinib**

Dasatinib (Sprycel, Bristol-Myers Squibb) is an adenosine triphosphatase (ATP)–competitive, dual specific Src, and Abl-kinase inhibitor. Src activation may play a role in the development and progression of many tumors. Src kinase modulates signal transduction through multiple oncogenic pathways, including platelet-derived growth factor receptor (PDGF-R), vascular endothelial growth factor receptor (VEGF-R), and others.

Dasatinib is not related structurally to imatinib; it is 325 times more potent than imatinib as an inhibitor of Bcr-Abl kinase activity. Dasatinib binds to both the inactive and active configuration of Bcr-Abl. It induces significant inhibition of the kinase activity of cells transfected with the wild-type Bcr-Abl as well as almost all mutants of Bcr-Abl except the T3151 mutation.

In phase 1 studies, dasatinib 15 to 180 mg orally daily and 35 to 90 mg orally twice daily showed excellent anti-CML activity. In chronic-phase CML, the rate of complete hematological responses was 90% and the rate of cytogenetic responses was 50%. Significant side effects included myelosuppression in 40% to 60% of patients and pleural effusions in 10%. Responses were observed in a wide variety of mutations.

In phase 2 studies, dasatinib 70 mg, given orally twice daily in chronic, accelerated, and blast phases after the failure of imatinib treatment, resulted in a favorable review by the FDA’s Oncology Drugs Advisory Committee for the treatment of Ph-positive CML (in all phases after imatinib resistance or toxicity) and of Ph-positive ALL.

A comparison of dasatinib with high-dose imatinib after the failure of standard-dose imatinib showed better results.

**Nilotinib**

Nilotinib (Tasigna, Novartis), a selective potent tyrosine kinase inhibitor of Bcr-Abl, is 20 to 50 times more potent than imatinib. Like dasatinib, it also suppresses the growth of all imatinib-resistant CML mutants except the T3151 mutation.

In a phase 1 study, nilotinib 400 mg orally twice daily was the dose-limiting toxicity. The maximum tolerated dose produced myelosuppression in 20% to 25% of patients and led to indirect bilirubin increases.

In chronic-phase CML, after the failure of imatinib therapy, the complete hematological response rate was 92% and the cytogenetic response rate was 50%. Phase 2 FDA pivotal trials are in progress.

Several other tyrosine kinase inhibitors (SK 1605, INN 0406, MK 0457, AT 9283, and KW 2449) are in phase 1 studies.

**Hypomethylating Strategies in Leukemia and Myelodysplastic Syndromes: An Update**

**Presenter:** Hagop Kantarjian, MD, Chairman and Professor, Leukemia Department, University of Texas MD Anderson Cancer Center

Global and site-specific DNA methylation induces suppression of regulatory genes, which promotes tumor progression and resistance. Protein or histone deacetylation also contributes to this process. Two classes of agents may suppress these processes:

- hypomethylating agents: 5-azacytidine (Vidaza) and decitabine (Dacogen, Pharmachemie B.V. Haarlem/MGI Pharma)
- histone deacetylase inhibitors: valproic acid, depsipeptide (FK 228, Fujisawa), vorinostat (Zolinza, Merck; formerly, suberoylanilide hydroxamic acid [SAHA]), and others

5-Azacytidine has been approved for the treatment of MDS and chronic myelomonocytic leukemia (CMMl), and decitabine was recently approved for the treatment of MDS and CMML. Ongoing studies include first-line therapy with decitabine in elderly AML patients, decitabine maintenance in AML patients, first complete remissions (CRs), and decitabine combinations, particularly with valproic acid and other histone deacetylase inhibitors.

The combination of decitabine plus valproic acid has been studied in a phase 1/2 study. A fixed dose of intravenous (IV) decitabine 15 mg/m², given over one hour daily for 10 days, was combined with escalating doses of valproic acid. The maximum tolerated dose of valproic acid was determined to be 50 mg/kg orally daily when given concomitantly with decitabine.

Most adverse reactions were related to valproic acid administration, mainly neurotoxicity. Twelve patients (22%) had objective responses, including 10 CRs (19%), and 3% CRs with incomplete platelet recovery. The duration of remission was 7.2 months. Overall survival was 15.3 months.
Future studies will include the combination of decitabine with vorinostat and LBH589. Both agents are potent hydroxamic acid derivatives with activity in cutaneous lymphoma. The combination of 5-azacytidine, valproic acid, and all-trans retinoic acid is under study in patients with high-risk MDS and AML. This combination was safe and had significant activity with a CR/incomplete platelet recovery rate of 58% in 12 older patients.

Another ongoing study in MDL/AML patients includes the combination of 5-azacytidine and MGCD 0103, an oral histone deacetylase inhibitor.

**Melphalan, Arsenic Trioxide, and Ascorbic Acid for Multiple Myeloma**

**Presenter:** James Berenson, MD, Medical and Scientific Director, Institute for Myeloma and Bone Cancer Research, West Hollywood, California

Multiple myeloma (MM) is an incurable B-cell malignancy, and resistance develops in nearly all patients. Most patients develop renal insufficiency, which is associated with poor survival.

Arsenic trioxide (Trisenox, Cephalon) is an active antimalyeloma agent. Ascorbic acid enhances the cytotoxic action of melphalan (Alkeran, GlaxoSmithKline). A combination of these three agents (known as the MAC regimen) was used in a prospective, multicenter, single-arm phase 2 study to determine the objective response rate, progression-free survival, safety, and tolerability in relapsed or refractory MM patients.

Secondary objectives included time to response, overall survival, and renal effects.

Patients received melphalan 0.1 mg/kg orally, arsenic trioxide 0.25 mg/kg IV, and ascorbic acid 1 g IV on days one through four of the first week. Arsenic trioxide and ascorbic acid twice weekly were given in the second to fifth weeks, and the rest of the regimen was given during the sixth week of cycle one.

Melphalan was given on the first to fourth days, and arsenic trioxide and ascorbic acid were given twice weekly in the first to fifth weeks. The rest of the regimen was given during week six of the second through sixth cycles.

Objective responses were observed in 31 patients (48%), including two CRs, 15 partial responses, and 14 minor responses. The median progression-free survival was seven months, the time to response was 1.5 months, and overall survival was 19 months.

Of the 22 patients with elevated serum creatinine levels, 18 (82%) showed a reduction in these levels. Grade 3 or 4 anemia and resistance develops in nearly all patients. Most patients experience complete remissions (CRs) with no evidence of minimal residual disease in the bone marrow. Seven of the 10 patients showed no adenopathy in the peripheral nodes. Grade 3 neutropenia was noted in six patients; grade 4 lymphopenia, in seven patients; and CMV reactivation.

B-cell CLL results from the relentless accumulation of small, mature, slowly dividing monoclonal B lymphocytes. It is one of the most common forms of leukemia in the U.S., with an annual incidence of 3.4 per 100,000 people. The disease remains incurable.

The reported single-agent activity of alemtuzumab (anti-CD52, Campath-1H, Berlex) and rituximab (anti-CD20, Rituxan) for CLL and the preliminary data suggest the existence of potential synergy between these two monoclonal antibodies. These findings provided the rationale for combining them in a pilot study of previously untreated CLL patients.

Treatment consisted of the simultaneous subcutaneous administration of alemtuzumab 30 mg three times weekly for 18 weeks plus rituximab 375 mg/m² IV every two weeks for eight weeks. Ten patients (median, age 52 years) received trimethoprim/sulfamethoxazole (Bactrim, Women First) and valacyclovir (Valtrex, GlaxoSmithKline) with fluconazole (Diflucan, Pfizer) to protect against potential cytomegalovirus (CMV) reactivation.

After a median of 10 months (range, 6–13 months), all 10 patients experienced complete remissions (CRs) with no evidence of minimal residual disease in the bone marrow. Seven of the 10 patients showed no adenopathy in the peripheral nodes. Grade 3 neutropenia was noted in six patients; grade 4 lymphopenia, in seven patients; and CMV reactivation, in four patients.

Future studies are planned to include a larger population of CLL patients.

**Chemotherapy with or without Oblimersen Sodium in Advanced Chronic Lymphocytic Leukemia: Update**

**Presenter:** Kanti Rai, Joel Finkelstein Cancer Foundation Professor of Medicine, Albert Einstein College of Medicine, Bronx, New York, and Chief, Division of Hematology/Oncology, Long Island Jewish Medical Center, New Hyde Park, New York

Bcl-2 is an anti-apoptotic protein that has been closely linked to chemotherapy resistance and inferior survival in patients with CLL. Oblimersen sodium (Genasense, G 3139, Genta) is an antisense drug that blocks the production of specific proteins. As an oligonucleotide that targets Bcl-2, oblimersen enhances apoptosis induced by fludarabine (flu, Fludara), dexamethasone, and rituximab (Rituxan) in cultured CLL cells. Flu, a purine analogue, can be given both orally and intravenously. Flu inhibits DNA synthesis by interfering with ribonucleotide reductase and DNA polymerase. It is active against both dividing and resting cells.

A multicenter, multinational, randomized study of 241 patients was conducted to determine whether the addition of oblimersen to Flu/cyclophosphamide (Cy, Cytoxan) could
increase the proportion of CLL patients who achieved complete or nodular partial responses (CR/nPRs).

All patients received Flu 25 mg/m² per day plus Cy 250 mg/m² per day each day for three days every month for a maximum of six cycles. Patients receiving oblimersen received 3 mg/kg per day for seven days by IV infusion, beginning four days before Flu/Cy and on each day of Flu/Cy treatment. Response assessments were conducted at every cycle during treatment and every two months thereafter for up to 36 months.

The primary endpoint was a comparison of the proportion of patients who achieved CR/nPRs by National Cancer Institute Working Group (NCI–WG) criteria. Patients with evidence of disease, as confirmed by computed tomography, required clearance to be enrolled in the study. Secondary endpoints included overall response rates (i.e., CRs, nPRs, and PRs); durable responses; response duration; time-to-progression; clinical benefit; and safety.

Twenty patients (17%) achieved a CR/nPR when oblimersen was added to the Flu/Cy (n = 120), compared with eight patients (7%; 121 patients) receiving Flu/Cy alone (P = .025). A significantly higher relapse rate was noted in patients who achieved a CR/nPR with Flu/Cy alone compared with oblimersen patients (75% vs. 25%, respectively).

Patients receiving oblimersen who achieved a CR/nPR showed a significant increase in the duration of remission without achieving a median value. The median follow-up in the oblimersen group was 30.9 months, whereas the median follow-up in the patients receiving chemotherapy alone was 20.8 months (P = .035).

CR/nPR response status also tended to be associated with less minimal residual disease with the addition of oblimersen, as assessed by standard flow cytometry analysis. An increased incidence of reversible thrombocytopenia, pyrexia, nausea, vomiting, and fatigue were noted when oblimersen was added.

The patients most likely to benefit from the addition of oblimersen had not been previously resistant to Flu, had received one or two prior treatment regimens, and had responded to their last treatment for six months or more. The addition of oblimersen to Flu/Cy thus resulted in an increased number of durable CRs and nPRs as well as an increased proportion of patients who were alive at three years. The best results were observed in chemosensitive patients, characterized by a four-fold rise in the rate of CRs/nPRs, significantly longer survival, and a lower incidence of neutropenia and anemia.