Yttrium 90 Ibritumomab Tiuxetan Radioimmuno-
therapy in Relapsed or Refractory Non-Hodgkin’s
Lymphoma

According to an analysis of long-term responders, yttrium 90 (90Y) ibritumomab tiuxetan (Zevalin®, Biogen Idec) radioimmunotherapy produces durable long-term remissions, with time to progression (TTP) of disease being greater than 12 months, in patients with relapsed or refractory B-cell non-Hodgkin’s lymphoma (NHL).

Between 1996 and 1999, 211 patients with relapsed, refractory, or transformed indolent B-cell NHL were treated in four trials of 90Y ibritumomab tiuxetan. With a longer follow-up period, there was evidence of long-term durable responses.1

To further characterize the patients with long-term responses, patients with time to progression of 12 months or longer were identified. By this defined criterion, durable responses were achieved in 38% of the patients (78 of 211 patients). The median age of these patients was 58 years; 44% were over age 60 and 55% were men. Seventy-six percent of this group had follicular lymphoma, and 41% had lymphoma-tous marrow involvement. A high percentage of these patients had undergone three or more previous therapies.

The complete response (CR) or complete response unconfirmed (CRu) rate in long-term responder (LTR) patients was 65%. In this group, the median duration of response was 29.3 months, and the time to progression was 31 months. Overall, the median duration of response in LTR patients (28.1 months) compared favorably with the duration of response to the last prior therapy for LTR patients (12 months).

At the time of this analysis, the median follow-up period was 45.6 months, with some responses lasting more than 75 months. The median duration of response in ongoing responders to date was 48 months, and the time to progression of disease was 50.4 months.

Oblimersen Sodium Alone and with R-CHOP
Mantle-Cell Lymphoma

Oblimersen sodium (Genasense™, Genta) is an antisense drug that blocks the production of Bcl-2, a cancer protein that contributes to the inherent resistance of cancer cells to anticancer treatment. It is well tolerated and has a modest but clear single-agent activity in patients with mantle-cell lymphoma, an aggressive form of NHL that is highly resistant to chemotherapy and generally considered incurable with conventional treatment. This drug can also be safely added to therapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), bringing about responses in all patients treated to date.

A study was designed to evaluate the effects of escalating doses of oblimersen sodium used alone, without chemotherapy, in both patients with newly diagnosed disease and in previously treated patients receiving 3 mg/kg per day for seven days every 21 days, up to a maximum of six cycles.
Upon progression of disease, patients with newly diagnosed mantle-cell lymphoma who had not received chemotherapy were given oblimersen sodium plus R-CHOP for up to six cycles. Patients who had not responded to chemotherapy initially received the lowest dose of oblimersen sodium (3 mg/kg per day for six cycles) and were then given 4 mg/kg per day for seven days for subsequent cycles. A cohort, previously started at 4 mg/kg per day for cycle 1, was switched to 5 mg/kg per day for subsequent cycles.

A total of 47 patients were enrolled; 19 were new to chemotherapy and 28 had lymphoma that had relapsed from or had been refractory to earlier treatment. The primary endpoint was the overall response rate. Secondary endpoints included safety, CR rates, time to disease progression, and survival.

Across all treatment groups, of the 33 evaluable patients, 11 (33.3%) remained stable without disease progression during all six treatment cycles of oblimersen sodium alone. To date, of the 12 evaluable chemotherapy-naive patients with newly diagnosed mantle-cell lymphoma who completed oblimersen sodium plus R-CHOP therapy, four patients experienced CRs, three with CRs and one with a CRu; six patients had partial responses (PRs); and the remaining two patients had stable disease. In the 21 evaluable patients whose condition had relapsed or was refractory to earlier treatment, two patients had CRs (one a CR and one a CRu), one patient had a PR, nine patients had stable disease, and nine patients experienced disease progression.

Oblimersen sodium did not appear to increase the toxicity of R-CHOP. Furthermore, in the previously treated patients who received monotherapy, escalating doses of this drug, from 3 mg/kg per day up to 5 mg/kg per day in subsequent cycles, appeared to be well tolerated.

Tipfarnab in Poor-Risk Patients with Acute Myeloid Leukemia and Myelodysplastic Syndrome

Speaker: Jeffrey E. Lancet, MD, Assistant Professor of Medicine, James P. Wilmot Cancer Center, Rochester School of Medicine and Dentistry, and Admitting Physician, Strong Memorial Hospital, Rochester, New York.

Interim results from a phase 2 clinical trial indicate that tipfarnab (Zarnestra™, Johnson & Johnson), a novel farnesyl transferase inhibitor, has beneficial activity in previously untreated poor-risk patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).

Farnesyl transferase inhibitors, which competitively block farnesyl protein transferase, are being developed and tested across a wide range of refractory acute leukemias. In this study, patients with poor-risk AML, MDS, or chronic myelomonocytic leukemia (CMML), were eligible.

A total of 104 patients—94 with AML, four with MDS, and six with CMML—received tipfarnib 600 mg twice daily for 21 days, followed by a one- to three-week recovery period. Up to four cycles of the drug were permitted in patients with CRs. The primary endpoint was the overall response rate; secondary endpoints included toxicity rates and the determination of various molecular genetic and chemical correlates.

In the 92 patients who were evaluable for response, the overall response rate (RR + PR) was 33%. In patients older than 75 years of age, the overall response rate was 36%, with 26% having CRs and 10% having PRs. Overall, CRs occurred in 19 patients (21%) of this population. The median duration of response in the patients with CRs was 5.8 months.

The median overall survival was eight months for all patients. In the responders (CR + PR), however, the overall survival rate was not reached, with more than 60% of patients still alive at 15 months. In the nonresponders, the median overall survival was five months. Nine patients died during the study. The only serious drug-related adverse event was grade 4 toxicity, manifested mainly as neutropenic infection in 12 of 96 patients (13%).

Arsenic Trioxide in Myelodysplastic Syndrome

Speaker: Norbert Vey, MD, Hematologist, Department of Hematology, Institut Paoli-Calmette, Marseille, France, and Spokesperson for the Groupe-Francais des Myelodysplasies, France.

Preliminary results from a phase 2 clinical study suggest that an outpatient arsenic trioxide (Trisenox®, Cell Therapeutics, Inc. [CTI]) regimen is safe, well tolerated, and effective in patients with myelodysplastic syndrome (MDS).

Arsenic trioxide was given as a one-hour intravenous infusion, with a loading dose of 0.30 mg/kg per day for five days and a maintenance dose of 0.25 mg/kg per day twice a week for 15 or more weeks as an outpatient treatment. Disease assessment was performed every eight weeks.

The primary study objective was to determine the percentage of lower-risk patients who achieved major hematologic improvement after arsenic trioxide treatment and the percentage of higher-risk patients who achieved a complete or a partial remission or a major hematologic response after treatment. According to modified International Working Group criteria, the response must be maintained for 56 or more days.

A total of 82 patients with MDS were enrolled in the study; 74 patients (27 with a lower risk and 47 with a higher risk) were evaluable for response. Treatment with arsenic trioxide resulted in major or minor hematologic responses in almost 25% of patients with low-risk and high-risk myelodysplasia, and an additional 30 high-risk patients had stable disease for at least two months. Among the evaluable patients, 16 (22%), including 10 higher-risk and six lower-risk patients, achieved definite hematologic responses, with nine major and one minor responses in the higher-risk patients and three major and three minor responses in the lower-risk patients.

Responses were observed across all hematologic lineages in higher-risk patients and in two lineages in lower-risk patients, including major and minor erythroid, platelet, and neutrophil lineages. Eight of the patients with hematologic responses became transfusion-independent; two additional patients decreased their dependence on transfusions by 50%. Responses to arsenic trioxide were durable, lasting from 59 to 322 days during the study. The median duration of response was 107 days.

Renal Impairment with Multiple Myeloma Therapy

Speaker: Tahir Latif, MD, Fellow in Hematology/Oncology, Cleveland Clinic Myeloma Program, The Cleveland Clinic Foundation, Cleveland, Ohio.
An analysis of the relationship between renal impairment and bisphosphonate therapy, as part of a treatment regimen under study in patients with multiple myeloma, suggests that there was no difference in the incidence of renal impairment in patients who were receiving combination therapy with thalidomide (Thalomid®, Celgene) and bisphosphonate therapy with either zoledronic acid (Zometa®, Novartis) or pamidronate (Aredia®, Novartis). Although previous studies had shown a similar 1% incidence of renal impairment in multiple myeloma patients receiving either zoledronic acid or pamidronate as bisphosphonate therapy, a possible adverse interaction between thalidomide and zoledronic acid has been suggested, resulting in a higher incidence of renal impairment—up to 20%—in these patients.

To elucidate this relationship between thalidomide and bisphosphonates, investigators included all 80 patients with multiple myeloma who were enrolled in a phase 2 trial in a separate analysis to evaluate the safety and toxicity of liposomal doxorubicin (Adriamycin®, vincristine, and dexamethasone (Decadron®, Merck) in combination with thalidomide with three months of follow-up. Early in the trial, two patients died of myocardial infarction and progressive disease, respectively, and were excluded.

The decision to initiate monthly bisphosphonate therapy was made by the treating physician. In 75 evaluable patients, 31 received pamidronate, 26 received zoledronic acid, and 18 received no bisphosphonate therapy. Eleven of the 75 evaluable patients developed renal impairment during the study. Of these patients, four of the 31 were taking pamidronate, five of the 26 were taking zoledronic acid, and two of the 18 had no exposure to bisphosphonate therapy.

There was no overall difference in the prevalence of renal impairment between patients with newly diagnosed disease and previously treated patients or between the type of bisphosphonates used. Renal impairment was related to progressive disease in five patients, to dehydration or infection in two patients, and to bisphosphonate therapy in the remaining four patients.

Because most of the episodes of renal impairment were multifactorial, it is possible that aggressive treatment of confounding factors (such as infection, dehydration, and progression of disease) might prevent permanent renal dysfunction. Renal impairment, which was considered to be solely related to bisphosphonate therapy, almost always improved after patients discontinued taking the offending bisphosphonate and were switched to an alternative agent.

Hospitalization for Neutropenia in Patients with Non-Hodgkin’s Lymphoma

Speaker: John M. Brooks, PharmD, Associate Professor of Pharmacy, College of Pharmacy, The University of Iowa, Iowa City, Iowa.

Neutropenia is a common and costly complication of combination chemotherapy in patients with newly diagnosed non-Hodgkin’s lymphoma (NHL). It occurs most often during the first two cycles of treatment and has a significant effect on inpatient Medicare costs.

The national Surveillance, Epidemiology, and End Results (SEER) program and Medicare-linked databases were used to estimate the average Medicare cost of neutropenia hospitalization for elderly patients with NHL over the first course of chemotherapy and to determine whether the total neutropenia hospitalization costs varied by patient factors at the baseline evaluation. Included in the analysis were patients in the linked SEER and Medicare databases with a first primary diagnosis of NHL between 1991 and 1999, who were 66 years of age or older at the time of diagnosis, and who had continuous Part A and B Medicare benefits outside a health maintenance organization one year before diagnosis through the first course of chemotherapy.

A total of 7,516 of 35,063 patients met the study entry criteria. Of these patients, 1,895 underwent a total of 2,484 hospitalizations for neutropenia covering a period of 23,379 days. The mean cost for one hospital stay was $7,691. Among the 1,895 patients, 451 had multiple hospital stays as a result of neutropenia. The average total hospitalization cost for each NHL patient was $2,542. The cost of all of these hospitalized patients was $10,081.

Baseline clinical characteristics (e.g., type of chemotherapy, diagnosis year, SEER registry, presence of renal disease, and disease stage) affected total costs of hospitalization resulting from neutropenia. All of these baseline characteristics, plus being female, affected inpatient length of hospital stay for neutropenia.

Although granulocyte-colony-stimulating factor (G-CSF) (filgrastim) (Neupogen®, Amgen) does lower the incidence and duration of febrile neutropenia for patients undergoing chemotherapy, results from a related SEER study indicate that rates of early G-CSF use varied across the country and that giving less than the recommended duration of G-CSF therapy was common in clinical practice. Such inadequate dosing of G-CSF has been associated with first-course neutropenia hospitalization and suboptimal patient outcomes.

Palifermin for Oral Mucositis

Speaker: Christos Emmanouilides, MD, Adjunct Assistant Professor of Hematology and Oncology, Division of Hematology/Oncology, Department of Cancer Services, University of California, Los Angeles, Medical Center, Los Angeles.

The administration of palifermin (Amgen), a recombinant form of human keratinocyte growth factor, has been shown to reduce the incidence and duration of severe oral mucositis. The agent also decreases patient-reported mouth and throat soreness, resulting in significant reductions in the use of health care resources, specifically days of hospitalization, the need for analgesics, and the incidence of parenteral feeding.

Oral mucositis is considered one of the most debilitating side effects of high-dose chemotherapy with or without total body irradiation and peripheral blood progenitor cell transplants used to treat patients with hematologic malignancies. In a recent phase 3 trial, palifermin therapy was shown to lower the incidence of severe oral mucositis, compared with placebo, and to reduce the duration of the event by almost one week (3.7 days) compared with placebo (10.4 days).

Palifermin therapy also helped to protect patients from grade 4 mucositis, the most severe form of this condition. Three
times fewer palifermin-treated patients (20%) experienced this debilitating side effect, compared with patients receiving placebo (62%).

To assess the value of palifermin treatment in decreasing health-utilization costs, the researchers performed an additional analysis of the data from this phase 3 clinical trial. The use of resources included the number of days of hospitalization, the number of days of analgesic use, the incidence and number of days of parenteral feeding, the incidence of intubation, and the incidence of infections and number of days of anti-infective therapy. These evaluations were made, without adjustments for multiple comparisons, in patients with all baseline measures who received at least one dose of the study drug during the trial. This included all 212 patients who had originally been enrolled in the study.

These additional data from the phase 3 trial demonstrated that by reducing the severity and duration of oral mucositis with palifermin therapy, patients experienced shorter hospital stays (15.3 days) than those given placebo (17.3 days). Palifermin-treated patients required opioid analgesic agents for only 6.8 days; the placebo group needed them for 11.8 days. The palifermin patients were also less likely to need parenteral nutrition for severe oral mucositis (11% versus 43% for the placebo patients) and were less likely to need intubation (0.9% versus 3.8% for patients receiving placebo).

Cost-effectiveness of Fondaparinux After Hip Fracture Surgery

Speaker: Sean D. Sullivan, MD, Associate Professor, Departments of Pharmacy and Health Services, and Director, Pharmaceutical Outcomes Research and Policy Program, School of Pharmacy and Public Health/Community Medicine, University of Washington, Seattle, Washington.

Extended thromboprophylaxis with fondaparinux (Arixtra®, Sanofi-Synthelabo) after hip fracture surgery appears to be more cost-effective and to achieve greater clinical benefit than does therapy with enoxaparin (Lovenox®, Aventis).

The first of the specific inhibitors of factor Xa, fondaparinux is approved for the prevention of venous thromboembolism (VTE) in patients who are undergoing major orthopedic surgery, including extended prophylaxis following hip fracture surgery. A cost-effectiveness analysis was performed to compare extended prophylaxis with fondaparinux versus enoxaparin on the basis of efficacy and safety data drawn from head-to-head clinical trials and the published literature.

The cost-effectiveness analysis was carried out from the perspective of U.S. health care payers. Costs were obtained from U.S. health care databases and were adjusted to 2003 dollars. Drug costs were based on wholesaler acquisition costs as of May 2003. The analysis took into account efficacy and long-term safety outcomes at 30 days, 90 days, one year, and five years after patient discharge. The main outcome measure was the prevention of VTE, defined as symptomatic deep vein thrombosis (DVT) and nonfatal pulmonary embolism (PE).

For a hypothetical cohort of 10,000 patients with hip fracture undergoing surgery and treated for 28 days with fondaparinux instead of enoxaparin, it was assumed that an additional 204 symptomatic venous thromboembolism events would be prevented at 30 days after surgery. These figures comprise 82 prevented deaths caused by PE, 45 nonfatal PE events, and 77 DVTs prevented.

The incremental cost of fondaparinux that would be gained by the use of extended prophylaxis per life-year with fondaparinux over that with enoxaparin is $694 at 30 days, $512 at 90 days, $940 at one year, and $2,573 at five years. At 30 days, the incremental cost of fondaparinux per life year saved falls well within acknowledged parameters for reasonable health care expenditures. At 90 days, one year, and five years after hip fracture surgery, fondaparinux was a dominant therapy compared with enoxaparin.

Enoxaparin for Thrombophilia and Recurrent Pregnancy Loss

Speaker: Benjamin Brenner, MD, Associate Professor of Hematology, The Bruce Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel.

Enoxaparin (Lovenox®, Aventis), a well-known, low-molecular-weight heparin, has been shown to be safe and comparatively effective in preventing miscarriages in thrombophilic women with a history of recurrent pregnancy loss.

It is estimated that recurrent pregnancy loss affects 2% to 5% of all couples desiring children. Maternal thrombophilia, a blood disorder that poses an increased risk of thrombosis, has been associated with recurrent pregnancy loss. Researchers performed a multicenter, prospective, randomized trial to investigate the use of an anticoagulant therapy with enoxaparin for improving pregnancy outcomes in these women.

In all, 183 patients were enrolled in the study at five to 10 weeks of gestation. The women were grouped according to type of thrombophilia, trimester distribution, and number of previous pregnancy losses, including three or more losses in the first trimester, two or more in the second trimester, and one or more in the third trimester. Treatment with enoxaparin 40 mg/day and 80 mg/day (40 mg twice daily) was given throughout the pregnancy and the postpartum period. The primary efficacy endpoint was delivery of a live, healthy infant. Safety endpoints included bleeding episodes in the newborns and thrombocytopenia in the mothers.

Enoxaparin therapy significantly increased the rate of live births, compared with the patients’ historical rates of live birth (81.4% vs. 28.2% for enoxaparin 40 mg and 76.5% vs. 28.3% for enoxaparin 80 mg). Treatment with enoxaparin also decreased the rate of pre-eclampsia and placental abruption. It is also noteworthy that no instances of maternal or neonatal bleeding were observed.

Aspirin for Polycythemia Vera

Speaker: Raffaele Landolfi, MD, PhD, Professor of Medicine, Istituto di Medicina Interna e Geriatria, Università Cattolica, and Director, Clinical Service for Coagulation Disorders, A. Gemelli Hospital, Rome, Italy.

The use of low-dose aspirin has been found to significantly reduce the risk of thrombosis in patients with polycythemia vera, a disorder marked by an abnormal increase in red blood
cells (RBCs) resulting from excess production by the bone marrow. Patients with polycythemia have an increased tendency to form blood clots that can lead to heart attacks or strokes.

In an attempt to find a treatment to improve upon the present method of cytoreduction—removing some of the patient’s blood periodically—the Efficacy and Safety of Low Dose Aspirin in Polycythemia Vera (ECLAP) Study was designed to test the effect of low-dose aspirin (100 mg daily) in patients with polycythemia vera. Initially, 1,630 patients were enrolled in this multicenter, parallel, double-blind, randomized clinical trial from 12 countries, including 11 patients from Europe and Israel. Of these, 512 patients were judged to have no clear contraindication to aspirin treatment and were randomly assigned to receive a 100-mg daily dose of aspirin or placebo. Sixty percent of the study participants were men, with a mean age of 61 years, who had the disease for an average of seven years. The follow-up duration was about three years.

For the primary study endpoints, treatment with low-dose aspirin significantly lowered the risk of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and all major arterial and venous thromboses. In addition, the risk of minor thrombotic events was significantly decreased. Major, total, and gastrointestinal bleeding episodes were slightly but not significantly increased.

REFERENCES

