Thalidomide and Multiple Myeloma

The effectiveness of thalidomide (THL) (Thalomid, Celgene) has been widely demonstrated in patients with relapsed or refractory multiple myeloma. In a prior study, Ibrahim Yakoub-Agha, MD, et al. observed that a higher incidence of drug-related toxicity greater than grade 2 was directly related to both the dose intensity and the cumulative dose of THL. At the same time, the rates of overall survival and event-free survival were not related to the mean daily THL dose received during the initial 90-day treatment period. This suggested that a lower dose (100 mg/day) might offer efficacy similar to that of the commonly administered higher dose (400 mg/day) but with fewer adverse effects.

Given the poor prognosis of these patients and the known potentiation of THL by dexamethasone (DEX), the study protocol called for administering a THL/DEX combination for patients who had not responded to treatment at any time or for those whose disease remained stable after three months of THL therapy. The primary endpoint was overall survival at one year.

One hundred ninety-five patients received THL 400 mg/day, and 205 patients received 100 mg/day. Reporting the first data of the final analysis, Dr. Yakoub-Agha stated that the inferiority hypothesis for the 100-mg/day dose was rejected. Although DEX was added to treatment more often for the 100-mg/day patients (109 vs. 90 patients for 400 mg/day), overall survival rates at one year were similar between the groups (73% for patients taking 400 mg/day and 69% for those taking 100 mg/day). Adverse effects, however, were fewer in the patients receiving 100 mg/day. The incidence of somnolence, peripheral neuropathy, and constipation was significantly lower with the lower dose. Dr. Yakoub-Agha concluded that survival was comparable with the two doses, but the 100-mg/day dose was better tolerated.

When a member of the audience asked, “Would you recommend, outside of a clinical trial, to begin treatment right away with 100 mg of THL/DEX?” Dr. Yakoub-Agha answered:

“Yes. I think that would now be the new treatment combination.”

Imatinib and Chronic Myelogenous Leukemia

An earlier analysis has shown that chronic myelogenous leukemia (CML) patients who experience at least a 3-log reduction in Philadelphia+ chromosome transcripts after a year of treatment with imatinib (ST1571, Gleevec, Novartis) had no disease progression at 24 months. The most important finding from an updated analysis of the International Randomized trial of Interferon/Ara-C (cytosine arabinoside) versus ST1571 (IRIS), a trial of imatinib versus interferon, was that these strongly responding patients may experience even further eradication of disease after four years.

Presenting the IRIS data, professor John Goldman, MD, of the Imperial College in London, United Kingdom, explained:

“It’s important to understand this concept that the higher the number of the log reduction, the fewer the transcripts in peripheral blood are found in the individual person.”

He noted that with a 2-log reduction in leukemia cells (bcr–abl transcripts), detected through real-time quantitative polymerase chain reaction (PCR) analysis, the patient’s status became negative for the Philadelphia chromosome. With a 3-log reduction, patients demonstrated major molecular responses. With a 4.5-log reduction, no transcripts were detected.

The analysis of 124 patients with PCR samples at four years showed that although 31% of patients had achieved a log reduction between 3 and 4 at one year, that reduction was found in 39% of the patients at four years. Similarly, the proportion of patients achieving a 4-log reduction grew from 22% at one year to 41% at four years. Dr. Goldman concluded:

“There is an optimistic possibility that the risk of disease progression might diminish with the passage of time.”

Rituximab and Chronic Lymphocytic Leukemia

“It has been known that rituximab [Rituxan, Biogen Idec] has activity, but not very good activity, in CLL [chronic lymphocytic leukemia],” stated Allessandra Ferrajoli, MD, from MD Anderson Cancer Center in Houston, Texas.

Antibody-dependent cytotoxicity is an important mechanism of monoclonal antibodies such as rituximab. Granulocyte–macrophage colony-stimulating factor (GM–CSF) (Leukine, Berlex) increases CD20 expression, the target of rituximab therapy. With promising evidence observed for the treatment of follicular lymphoma after combining rituximab with GM–CSF, Dr. Ferrajoli’s team enrolled patients with CLL into three groups:

• untreated patients, 70 years of age or older, with treatment indications from the National Cancer Institute Working Group

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During an eight-week cycle, all patients received intravenous (IV) rituximab 375 mg/m² once weekly for the first four weeks and GM-CSF subcutaneously on days one, three, and five for each of the eight weeks. Overall response rates were as follows: 86% for group 1; 80% for group 2; and 47% for group 3. Complete responses were observed in 7% of patients in group 1; in 14% of those in group 2; and in 6% of those in group 3.

Dr. Ferrajoli emphasized that some responses were seen in patients who had been heavily pretreated or who were genetically at higher risk. Treatment was well tolerated. Some grade 1 and 2 injection-site edema and bone pain with marrow expansion, seen in 11% of patients with better bone reserve, were attributed to GM-CSF.

Dr. Ferrajoli concluded: “GM-CSF priming increases CD20 expression in vivo with minimal toxicity. . . . It is associated with an encouragingly high response rate.”

Deferasirox for Sickle Cell Disease

A once-daily iron chelator may improve compliance in patients with sickle cell disease (SCD), potentially leading to a reduction in organ damage related to iron burden.

More than 90% of SCD patients have received transfusions by the time they reach 21 years of age, and approximately 37% of adults with SCD have hemosiderosis.

The iron chelator deferasirox (DFX) (Exjade, Novartis) is formulated as a dispersible tablet (e.g., in orange or apple juice). Its half-life of eight to 16 hours supports once-daily dosing.

DFX is metabolized by the liver. The current standard iron chelator, deferoxamine mesylate (DFO) (Desferal, Novartis), because it is excreted quickly, requires lengthy nightly subcutaneous infusions lasting eight to 12 hours. Compliance with iron chelation in patients with SCD has been shown to correlate with prolonged survival.

“There’s an unmet need for a safe, effective oral therapy for the treatment of iron overload,” stated the study’s lead author, Elliot Vichinsky, MD, from Children’s Hospital and Research Center in Oakland, California.

His study of DFX included 195 patients with SCD, two years of age or older, with histories of repeated transfusions and iron overload consisting of the following:

- serum ferritin (Fe) of 1,000 mcg/L or more
- liver iron concentrations of 2 mg of Fe per gram dry weight in patients receiving simple transfusions
- 5 mg or more of Fe per gram dry weight with exchange transfusions
- patients with relapsed or refractory active disease
- untreated patients with a Rai classification of stage 0 to II who were at high risk for disease progression
- patients with transfusional iron overload consisting of the following:
  - liver iron concentrations of 2 mg of Fe per gram dry weight with DFO.
  - serum ferritin (Fe) of 1,000 mcg/L or more.

The primary study objective was to assess the safety and tolerability of DFX. A secondary objective included changes in liver iron levels. The median age of the patients was 15 years (range, 3–54 years).

Mean hepatic iron was reduced as follows: by 1.3 mg of Fe per gram dry weight with DFX and by 0.7 mg of Fe per gram dry weight with DFO. Reductions in Fe were highest in patients receiving the highest doses of DFX (30 mg/kg) and DFO (50 mg/kg or more).

Adverse events were reported in 5.3% of the patients receiving DFX and in 3.2% of those receiving DFO. Increases in moderate-to-severe abdominal pain were noted in 12.9% of patients receiving DFX and in 4.8% of those receiving DFO. Moderate-to-severe diarrhea was observed in 6.1% of the DFX patients and in none of the DFO patients.

Dr. Vichinsky concluded that DFX removes iron from the body in proportion to the amount of drug administered; at 20 to 30 mg/kg per day, it maintains or reduces liver iron concentrations in most patients, similar to comparable DFO doses. He added that DFX use is likely to increase compliance and, therefore, to decrease the excess iron burden in patients.

Exjade was approved in the U.S. in November 2005.

Ibritumomab Tiuxetan and Lymphomas

Ibritumomab tiuxetan (90Y-IT) (Zevalin, Biogen Idec), the first radioimmuno therapeutic agent to receive FDA approval, consists of a monoclonal antibody linked to the radioactive isotope yttrium 90. After an infusion, the monoclonal antibody targets the CD20 antigen found on the surface of mature B cells and B-cell tumors.

At the ASH meeting, a series of small studies revealed safety and high 90Y-IT response and survival rates in non-Hodgkin’s and mantle-cell lymphomas. A cost-effectiveness analysis, comparing 90Y-IT monotherapy with rituximab monotherapy, tested the hypothesis that the radioimmunotherapy agent, despite its higher cost per dose, would not be the more expensive approach to achieving remission, according to Schering AG investigator, Sally Thompson, PhD. (Schering holds worldwide marketing and distribution rights for Zevalin; in the U.S., Biogen Idec retains marketing rights.)

With total costs and total months of remission taken into account, the analysis was based on the only existing monotherapy trials, by Gordon et al.2 for 90Y-IT and four-dose rituximab and by Ghielmini et al.3 for four-dose and eight-dose rituximab. In these trials of relapsed follicular lymphoma, the average duration of remission was 14.4 months with 90Y-IT, 6.2 months with the four-dose rituximab regimen, and 11.4 months with the eight-dose regimen.

The cost in euros (€) was 14,482€ per year for 90Y-IT, 19,084€ for the four-dose rituximab regimen, and 21,116€ for the eight-dose regimen, making 90Y-IT the most cost-effective approach. In U.S. dollars, the year’s costs to achieve remission were $17,529 for 90Y-IT, $23,099 for the four-dose rituximab regimen, and $25,559 for the eight-dose rituximab regimen.

REFERENCES