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## Fatigue: The Forgotten Symptom?

BY HEATHER LINDSEY

A new study shows that few oncologists are following the National Comprehensive Cancer Network guidelines for treating cancer-related fatigue in their patients with advanced disease. Here's the surprising news about the probable reasons. *Page 26*


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[ ALSO ]



PERIODICALS

# FDA Approval for Gleevec for Children with Ph+ ALL

The U.S. Food and Drug Administration has approved the use of Gleevec (imatinib) to treat children newly diagnosed with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). The tyrosine kinase inhibitor blocks the proteins that promote cancer cell growth and should be used in combination with chemotherapy to treat children with Ph+ ALL.

"Today's approval is the result of continuous interactions among the FDA, the Children's Oncology Group, and the National Cancer Institute to provide new and better treatments to American children with cancer," Richard Pazdur, MD, Director of the FDA's Office of Hematology and Oncology Products, said in a news release.

The safety and effectiveness of the drug's new indication were established in a clinical trial conducted by the Children's Oncology Group, sponsored by the NCI. The trial enrolled children and young adults one year and older with very high risk ALL, defined as patients with a greater than 45 percent chance of experiencing complications from their disease within five years of treatment.

The trial's 92 patients were divided into five treatment groups, with each successive group receiving a greater duration of Gleevec treatment in combination with chemotherapy.

Fifty of the Ph+ ALL patients received Gleevec for the longest duration, and 70 percent of these patients did not experience relapse or death within four years (event-free survival). Results also showed that patient deaths decreased with increasing duration of Gleevec treatment in combination with chemotherapy.

The most common side effects observed in the trial included decreased levels of neutrophils and blood platelets; liver toxicity; and infection.

Gleevec, marketed by Novartis, was granted accelerated approval in 2001 to treat patients with blast crisis, accelerated phase, or chronic phase Ph+ chronic myeloid leukemia that had failed to respond to interferon-alpha therapy. The drug has since been approved to treat: children newly diagnosed with Ph+ CML (2011) and adult patients after surgical removal of CD117-positive gastrointestinal stromal tumors.

## →MYELOMA

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percent, but none were grade 3 or 4. A PR or better was achieved in 34 percent of patients, with a median duration of response of eight months.

Tomer Mark (***Abstract 77***) reported the Weill-Cornell experience of POM/Dex with clarithromycin and 81 mg daily aspirin in 100 patients with relapsed myeloma (median three prior regimens, at least one with lenalidomide) with the response rate about 50 percent, VGPR or better was 22 percent, and median PFS of eight months. Grade 3 or 4 neutropenia was 40 percent, anemia was 25 percent, and fatigue was six percent.

These data set the stage for the late-breaking abstract (***LBA-6***) in which Meletios Dimopoulos presented the randomized trial of POM/Dex compared with the old high-dose DEX regimen in patients with myeloma refractory to both lenalidomide and bortezomib. There was a 2:1 randomization to POM (4 mg daily on days 1-21 of a 28-day cycle) + LoDex (40 mg weekly) or high-dose DEX (40 mg for 4 days on/4 days off x 3 every 28 days).

Patients over age 75 received 20 mg DEX in each arm. Patients (302 POM/Dex; 153 DEX) were heavily pretreated (median of five prior regimens), and 72 percent were refractory to both lenalidomide and bortezomib. With a median follow-up of 18 weeks, for the primary endpoint of PFS, use of POM/Dex resulted in about four months vs two months for DEX.

The interim planned overall survival analysis also favored POM/Dex (median not reached) vs DEX (34 weeks). Crossover to POM was permitted in the original design, and then mandated once the study endpoints were met.

Grade 3 or higher toxicities were neutropenia (42% POM/Dex vs 15%) and febrile neutropenia (7% vs 0%), with nearly equal thrombocytopenia (21% vs 24%) and infections (24 vs 23%). Neuropathy and VTE were rare (1% each).

While the question remains whether high-dose DEX is an appropriate comparator in the current era, we have gained a good picture of expected efficacy and toxicity of POM/DEX from these reports, and it is encouraging to see activity in patients refractory to lenalidomide.

Of course, efforts are already underway to build on POM/DEX. Paul Richardson reported (***Abstract 727***) a phase I trial determining that in patients with relapsed myeloma refractory to lenalidomide and exposed to but not refractory to bortezomib, full doses of bortezomib (1.3 mg/m² days 1, 4, 8, 11 every 21 days) plus DEX (20 mg day of and day after each bortezomib) can be combined with POM at 4 mg on days 1-14 of each three-week cycle. PR or better was achieved in almost 80 percent of patients. As expected, neutropenia was seen, but VTE seemed uncommon.

Another combination of POM/DEX with a proteasome inhibitor, in this case carfilzomib, was reported by Jatin Shah (***Abstract 74***). When combined with POM/DEX, the MTD for carfilzomib was 27 mg/m². In a heavily pretreated double-refractory population the response rate was about 50 percent, PFS was 7.4 months, and no grade 3 or 4 neuropathy occurred.

Antonio Palumbo (***Abstract 446***) also reported data on POM with prednisone as the corticosteroid in combination with cyclophosphamide in patients with relapsed myeloma previously treated with lenalidomide. With cyclophosphamide and prednisone each at 50 mg every other day, POM could be given at 2.5 mg daily and achieved a PR rate about 50 percent. In this study, maintenance POM continued and median PFS so far is 10 months.

### Novel 'Novel Agents'

We may finally, after a period of disappointment, be entering the monoclonal antibody era in myeloma. The plasma cell marker CD38 is an attractive target, and the unlabeled anti-CD38 monoclonal antibody daratumumab had no unexpected toxicities and has already demonstrated activity in a phase I trial in heavily pretreated patients. CS1 is a glycoprotein target expressed on plasma cells and NK cells. While the anti-CS1 antibody elotuzumab had minimal single-agent activity, it is synergistic in combination with lenalidomide, likely by enhancing antibody-dependent cytotoxicity (ADCC).

Paul Richardson (***Abstract 202***) also presented phase II data for patients with relapsed myeloma (1-3 prior therapies but no prior lenalidomide) who received lenalidomide at 25 mg on days 1-21 of a 28-day cycle with weekly Dex. (Rd) and weekly elotuzumab at either 10 or 20 mg/kg.

The overall response rate was 84 percent, with median PFS over two years, and a trend towards better results in the lower-dose cohort. Phase III trials of this regimen both in the front line and relapsed settings are under way. Tabalumab (A447), a monoclonal antibody against the TNF-family cytokine B cell activating factor (BAFF), has been combined with bortezomib-Dex with promising activity.

Agents with novel mechanisms of action that generated excitement by demonstrating activity in refractory patients included the kinesin spindle protein (KSP) inhibitor ARRY-520 (***Abstract 653***), the cyclin dependent kinase (cdk) inhibitor dinaciclib (***Abstract 76***) and the circularly permuted form of the apoptosis inducing ligand TRAIL (***Abstract 78***) that directly signals apoptosis.

Rapid progress continues in developing novel agents and combinations for myeloma therapy, now with the expectation of achieving a deep response with manageable toxicities not only in first-line but also in the relapsed setting. Still unanswered are how many and which drugs are optimal for induction, the role of high-dose chemotherapy with stem cell support to consolidate that remission, and the overall risk-benefit ratio for maintenance therapy. Additional investigation into prognostic factors, which change as therapy improves, and therapy for patients with high-risk disease is required.

"Still unanswered are how many and which drugs are optimal for induction, the role of high-dose chemotherapy with stem cell support to consolidate that remission, and the overall risk-benefit ratio for maintenance therapy."