Myeloproliferative Disorders

Highlights from the 44th Annual Meeting of the American Society of Hematology
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Simultaneous Oral Session Covers New Developments in Myeloproliferative Disorders

PHILADELPHIA—Several issues were raised at the oral session on myeloproliferative disorders at the ASH annual meeting, which was cochaired by **Ayalew Tefferi, MD**, from the Mayo Clinic, Rochester, and **Tiziano Barbui, MD**, from the Ospedali Riuniti, Bergamo, Italy. Some topics covered were: **Jaroslav Jelinek, MD, PhD**, from Baylor College of Medicine, Houston, discussed the diagnostic value of PRV-1 for polycythemias and thrombocytoses; **Lorraine Caruccio, MD**, from the NIH in Bethesda, provided a review of the correlation between high frequency single nucleotide substitutions and neutrophil surface protein expression in PRV-1 gene (CD177) polymorphisms; **Animesh Pardanani, MD**, of the Mayo Clinic, Rochester, MN, provided an update of an ongoing study using imatinib therapy for systemic mast cell disease, and **Jorge Cortes, MD**, from the MD Anderson Cancer Center, in Houston, discussed imatinib therapy for treatment of hypereosinophilic syndrome. In both of these early studies, imatinib appears to have some effect, although both authors noted that further study is required. **Ruben Mesa, MD**, also from the Mayo Clinic, presented data on a small study looking at the combination of low-dose thalidomide with prednisone for treatment of myelofibrosis with myeloid metaplasia. He reported that an objective clinical response was seen in 13/21 patients. **Bernd Hertenstein, MD**, from Hannover, Germany, presented very promising data on nonmyeloablative stem cell transplantation for myelofibrosis with myeloid metaplasia in elderly patients. This therapy resulted in a 1-year survival of 77%, with low treatment-related mortality. Hematologic responses were seen in 12/20 patients. Because this is a small group of patients, longer follow-up is necessary. Also in this session, **Steven Fruchtman, MD**, from Mount Sinai Medical Center in New York, presented the results of a long-term safety study of anagrelide (*see related story*). ■

ASH President Considers Future of Hematology in Clinical Practice

By Frieda Pearce, PhD

PHILADELPHIA—**Robert I. Handin, MD**, president of the American Society of Hematology (ASH), welcomed a large and enthusiastic audience to the 44th Annual ASH conference held in Philadelphia. For the nearly 20,000 attendees it was an informative meeting for hemostasis and thrombosis research. Dr Handin addressed the problem of the future of hematology in clinical practice. "Unfortunately, medical leaders or any of the myriad insurers and other third-party payers are either too busy or not sufficiently interested to attack the problem unless and until patients with complex hematological problems turn up at care centers that are devoid of hematological expertise. Let's hope it doesn't get that bad," he said.

Some of the solutions Dr Handin offered were to combine hematology practice with another specialty, such as medical oncology or clinical research. He suggested that hematologists embrace new technology and integrate it into practice, seek out and develop programs for orphan diseases, or be the first to apply new genetic knowledge or therapies. He also recommended that hematologists consider international health.

Attendees at the 44th annual meeting of ASH in December

Among the many stimulating sessions on myeloproliferative disorders during the 5-day conference were an update on IRIS, the trial with imatinib for CML; the results of a large, long-term safety study of anagrelide; and presentations on the PRV-1 gene as a potential marker for polycythemia vera and essential thrombocythemia. ■

Retrospective Study of 3660 Anagrelide Patients Shows Drug to Be Effective and Safe Over the Long Term

PHILADELPHIA—At the simultaneous session on treatment of myeloproliferative disorders at the ASH annual meeting, **Steven Fruchtman, MD**, of Mount Sinai School of Medicine, New York, presented data from a large, retrospective safety study of anagrelide. There were 3660 patients in the safety cohort (2251 ET and 1409 non-ET, of which 462 had PV). Patients were recruited to this study if they had a platelet count of ≥900,000/µL with no comorbidities or ≥600,000/µL with prior thrombotic events or attendant comorbidities. Complete response was measured as a reduction of platelet counts to ≤600,000/µL for the first group or ≤50% of baseline for the second group. Results of this study showed that if one includes partial responders (20%-50% reduction), the total response rates were 79% and 73%, respectively. Median time to response was 72 days, according to Dr Fruchtman.

Steven M. Fruchtman, MD, answered questions informally after the simultaneous session on MPDs.

The analyses also examined the leukemogenic potential of anagrelide. Dr Fruchtman noted that over 70% of MPD patients with thrombocytosis achieved control of platelet number. With a maximum follow-up of over 7 years in this large cohort of ET and PV patients, for the treatment duration analyzed so far anagrelide has not increased the incidence of leukemic transformation. Longer follow-up is required to confirm these important observations.

Two other abstracts at ASH dealt with long-term treatment with anagrelide. In one, the **Swedish MPD Study Group** reported on the use of

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Retrospective Study, *con't*

anagrelide in 60 patients for a 2-year period. Some of these patients had previously received other cytoreductive drugs, including HU and busulfan. They found that anagrelide was able to control the platelet count in 67% of the patients. The reported side effects were similar to those previously reported by the Anagrelide Study Group. The Swedish group indicated that at the average dose of 2.2mg/day, the doctors and patients scored feasibility above 9 on a 10-grade scale, although there was a 50% drop-out rate. The authors indicated that anagrelide is a valuable alternative to other platelet-reducing drugs.

In the other, **Hanna Rosenbaum, MD**, and **Jacob M. Rowe, MD**, both from Rambam Medical Center, Haifa, Israel, reported on anagrelide use in a small cohort of patients in which 70% had ET. They found no thrombotic complications or leukemic transformation in these patients. "Low-dose anagrelide is effective in reducing platelet counts in MPDs. However, the treatment is not benign, and careful monitoring of blood counts and cardiac follow-up are required during treatment," they concluded. ■

In the safety cohort of 3660 patients with a maximum follow-up of over 7 years, anagrelide did not increase the incidence of leukemic transformation.

Responding to Patients' Emotions Is Critical in Improving Physician/Patient Communications

In the ASH session entitled, *Enhancing Physician/Patient Communication Regarding Hematologic Disorders*, **Anthony Back, MD**, from the Fred Hutchinson Cancer Research Center, said, "Delivering bad news is a fundamental skill topic for hematologists, but it is quite rare that hematologists have formal training in this area. Doctors learn communication skills more likely through traumatic experience than training." Dr Back outlined a bad-news protocol for communicating with patients, which includes: preparation that allows for adequate time and appropriate information, awareness of what the patient already knows and what he/she is willing to acknowledge, and avoidance of medical jargon. "Respond to the patient's emotion, a step that is often skipped," said Dr Back.

Susan Block, MD, from the Dana-Farber Cancer Institute, discussed the importance of observing the patient's reaction and adjustment to the bad news. "One of the most important things is to tolerate their emotions when they express them. Acknowledge that you see that it is hard for them to hear the news—it will help them move along in the process of dealing with their emotions." There is also value in paying attention to your own emotional response to the patient. "If you are overwhelmed, get help and share the burden," concluded Dr Block.

Stephanie Lee, MD, from the Dana-Farber Cancer Institute, talked about the benefits of shared decision making. She cited the CML guidelines developed by ASH, which suggest that in determining the best treatment options, physicians should consider the medical facts and patient values. By asking the patient's opinion, the physician shows an interest in the patient and respect for the patient and involves the patient in his or her treatment.

The session was brought to a close by a former AML patient, **Susan K. Stewart**, the founder of the Blood & Marrow Transplant Information Network, who provided a patient perspective. Some patients busy themselves with information gathering to avoid dealing with their emotional difficulties. Others feel overwhelmed by information. Ms Stewart suggested taping the physician-patient discussion concerning diagnosis and treatment. This way the patients and their families can hear over again what the physician actually said. It is also important for the physician to encourage the patient to ask questions, both during the initial communication and later on. On the part of the patient, it is necessary to communicate, either by asking questions in person or using the phone or email. "Email allows patients to compose their thoughts in the privacy of their homes and avoids embarrassment," she said. "The physician can also help the patient put the illness in perspective by discussing pain and psychological stress, talking about options to cope with stress and anxiety, and encouraging communication," said Ms Stewart. ■

PV Patients with Gain of 9p Mutation Have Increased Risk of Leukemic Transformation

In a poster session at the 44th ASH annual meeting, **Mark Stein, MD**, **Steven M. Fruchtman, MD**, and **Vesna Najfeld, MD**, all from the Mount Sinai School of Medicine, and **Richard T. Silver, MD**, of the Weill Medical College of Cornell University, presented the prognostic implications of the gain of 9p mutation in PV patients. These patients were found to be at a younger age group at diagnosis (49 vs 60 yr). Transformation into AML and MF occurred in 11% of the patients respectively instead of the 6% and 4% reported by the Polycythemia Vera Study Group. There was also a lack of thrombotic events in this subgroup and is not correlated with worse survival. Based on their findings, they found that this was a unique group of PV patients and more such studies in PV patients are required.

Update on CML: Delaying Transplant Increases Mortality

"Transplant is the only curative approach for CML," **Jerald Radich, MD**, of the Fred Hutchinson Cancer Research Center in Seattle, said during an education program on CML at the 44th ASH annual meeting. Nevertheless, the success of imatinib in CML has revised the treatment strategy for CML patients. The prolonged cytogenetic remissions seen with imatinib therapy encourage its use as first-line therapy, even in those patients who may be good risks for transplant. Several factors affect the outcome of transplantation, a primary one being the stage of disease. Survival in the chronic phase is good, ranging from 60%-80% at five years, but survival rates decrease when patients are in accelerated phase (40%) or blast crisis (10%-20%). At the Fred Hutchinson Cancer Center, patients with advanced CML and newly diagnosed patients (median age 35 yr) were treated with a nonmyeloablative regimen and showed 85% survival, reported Dr Radich. The indication was that delaying transplant increases mortality. Molecular analysis to identify *bcr-abl* translocation and comparison of standard treatments with imatinib and transplant showed that imatinib failures do not achieve cytogenetic response. Only transplant results in complete molecular remission.

Treatment	Major remission	Mortality
Stem cell transplant	50%–85%	10%–50%
Imatinib	3%–6%	<1%

With patients in the advanced stages of disease, relapse is a distinct problem, and the choice of treatment requires careful evaluation. The early detection of minimal residual disease allows for earlier initiation of treatment when the disease burden is far less than at pathological relapse. Only a small percentage of those with accelerated phase disease achieve a complete response to imatinib or IFN. Some transplant patients with accelerated phase survive without relapse, whereas others relapse shortly after transplant. The different patterns of gene expression before transplant, ie, those genes that control cell cycle, apoptosis, drug resistance, and metabolism, may predict outcome of treatment.

In the accompanying table, the statistics of patient studies have been compared in terms of remission and mortality. Given that imatinib can produce cytogenetic remission, it may be important to harvest peripheral blood stem cells at the time of cytogenetic remission to be used in the future if the patient's disease progresses. Considering the ability of transplant to have the highest ratio of remission, Dr Radich suggested the patient be evaluated and considered for transplant, especially in advanced stages of the disease. ■

Satellite Symposium, *con't*

summary, they found that the six most frequent chromosomal abnormalities associated with PV are those of deletion in chromosome 20 and 17p, and abnormalities of chromosomes 9, 8, 13, and 1. Dr Fruchtman referred to a study by Sterkers et al, who reported that in a cohort of 17 patients who transformed to acute leukemia or MDS, seven patients had deletions of 17p and all seven had received HU. Three of the seven received only HU. Because the leukemia risk increases when HU is combined with other agents, "we have to be concerned about using sequential or combination therapy in these patients," Dr Fruchtman said.

John McCarty, MD, discussed transplant issues in MPDs during the satellite symposium.

Transplant issues in MPDs

John McCarty, MD, from the Virginia Commonwealth University Medical College of Virginia, Richmond, discussed the controversial treatment of stem cell transplant for chronic MPD patients, particularly those with IMF. IMF is characterized first by marrow fibrosis and may proceed to osteosclerosis. IMF patients are very often hypermetabolic and, in the later stages, become transfusion dependent, have pancytopenia and clear symptoms of massive organomegaly, and very frequently inaspirable marrow.

There are a number of therapeutic options for the treatment of IMF, including supportive care, steroids, growth factors, and interferon-α. "Splenectomy has also been advocated as a therapeutic intervention for some selected patients with specific issues," Dr McCarty said. It has been shown to be most effective in patients who develop painful organomegaly either from infarct or from compressive syndromes. However, the risks of complication and mortality are fairly high at about 10%-15%.

Another treatment strategy is to replace the stem cell, Dr McCarty explained. Initial studies of stem cell transplant reported by Anderson and colleagues from the Fred Hutchinson Cancer Center tried matched donor transplant. There was about a 60% survival with anywhere from a 1-7 year follow-up in this cohort of patients. A French study also reported 71% survival and event-free survival of 59% at 4 years. Given the relatively high rate of transplant-related mortality and the overall morbidity of the allogeneic procedure, attention was turned to autologous transplant as another therapeutic option. In a retrospective study of 21 patients who underwent high-dose chemotherapy and peripheral blood stem cell transplantation, the 2-year actuarial survival was about 61%.

The more recent application of non-myeloablative stem cell transplantation may play a role in minimizing transplant-related mortality. In a small study underway of four patients aged 48-58 years who underwent a nonmyeloablative stem cell transplantation preparative regimen of fludarabine and melphalan, all patients were grafted by day 14. At 14 months follow-up, all patients were alive without evidence of disease and, more importantly, all patients had resolution of splenomegaly. This approach is very promising, but the numbers are small and the follow-up is fairly short.

Splenectomy before transplant is another area of controversy. Recovery from transplant for previously splenectomized patients has been found to be more rapid. "What argues against applying splenectomy as a blanket recommendation for all patients undergoing transplant for myelofibrosis is the operative mortality rate approaching 10%," said Dr McCarty. He concluded that, "unless patients have significant symptomatic splenomegaly, refractory hemolytic anemia, or complications of portal hypertension, which cannot be managed medically, they should not be routinely offered splenectomy." ■