Consolidation with Arsenic Trioxide Significantly Improves Event-free Survival and Overall Survival Among Patients with Newly Diagnosed Acute Promyelocytic Leukemia

Arsenic trioxide is an effective and indicated agent for relapsed acute promyelocytic leukemia (APL). A study now demonstrates that arsenic trioxide has clinical benefit for patients with newly diagnosed APL. Bayard L. Powell, MD, the Comprehensive Cancer Center of Wake Forest University, reported findings from the study in which arsenic trioxide was given as consolidation therapy to patients with APL who had complete remission following standard induction therapy.

The study involved 480 adults (15-79 years old) and 57 children (<15 years old). Adult patients who had complete or partial remission after induction therapy were randomly assigned to receive two 25-day courses of arsenic trioxide (0.15 mg/kg/day) as a first consolidation therapy (followed by standard consolidation therapy; n=243) or to receive standard consolidation therapy (n=237). Children received the same induction therapy and standard consolidation therapy; arsenic trioxide was not offered to children because its safety had not been defined in this population at the time of accrual to the study. Data on children were analyzed separately.

The estimated 3-year event-free survival rate was significantly better for patients who received consolidation therapy with arsenic trioxide (81% vs 66%; p=0.0007). The estimated overall survival rate was also significantly better for this group of patients (86% vs 79%; p=0.063). The 3-year event-free and overall survival rates for the group of children were not significantly different from those for adults who did not receive arsenic trioxide (62% and 86%, respectively).

The response rate was similar for all patients (adults and children). Dr. Powell noted that the rate of complete remission was significantly lower for patients who had high-risk disease (defined as a white blood cell count of more than 10,000) compared with the rate for patients with low- or intermediate-risk disease. In addition, the rate of death during induction and the relapse rate (within 1 year) were higher for patients with high-risk APL. "There were a substantial number of early events during induction, but once patients achieved remission, the shapes of the curves are similar for all three groups," Dr. Powell explained.

Dr. Powell said that treatment with arsenic trioxide was associated with acceptable toxicity. Grade 4 hematological toxicity occurred during consolidation therapy in 55% of patients treated with arsenic trioxide and in 67% of patients who received only standard consolidation therapy. Grade 4 nonhematological toxicity occurred in 5% of patients in both groups.

A Randomized, Controlled, Double-Blind Phase 3 Study of Bevacizumab/Interferon-α2a vs Placebo/Interferon- α2a as First-line Therapy in Metastatic Renal Cell Carcinoma

The AVOREN trial was conducted to compare interferon alone with interferon plus bevacizumab for the treatment of metastatic renal cell carcinoma (RCC). The findings of the trial represent an important step in the recent advances in the treatment of RCC.

"In this placebo-controlled study, the addition of bevacizumab to interferon results in clinically important and statistically significant improvement in progression-free survival and tumor response," said Bernard Escudier, MD, Institut Gustave Roussy, France, who reported the findings of the study. The antiangiogenic agent, which targets vascular endothelial growth factor (VEGF), joins two other VEGF inhibitors, sunitinib and sorafenib, as effective agents for metastatic RCC.

Dr. Escudier explained that analysis of tissue samples from several different types of cancer has demonstrated that RCC is associated with the greatest expression of VEGF. In a phase 2 trial, bevacizumab (10 mg/kg) significantly improved the time to progression after failure of cytokine therapy.

The multicenter trial included 649 patients with advanced RCC who had undergone nephrectomy. The patients were randomly assigned to treatment with interferon (9 MIU, subcutaneously, three times per week) plus bevacizumab (10 mg/kg, intravenously, every two weeks; n=322) or the same dose of interferon plus placebo (n=327). The primary endpoint was progression-free survival (PFS).

Dr. Escudier reported that tumor response and PFS were significantly better in the interferon plus bevacizumab arm than in the interferon alone arm. In the 595 patients who had measurable disease, tumor response occurred in 31% of patients who received the combination

therapy and in 13% of patients who received interferon alone ($p < 0.0001$). The median PFS was 10.2 months for the combination therapy and 5.4 months for interferon alone.

Dr. Escudier explained that PFS was also evaluated in patient subgroups stratified according to Motzer score. For patients who had a favorable or intermediate Motzer score, the PFS was significantly better for interferon plus bevacizumab than for interferon alone. However, for patients with a poor score, there was no significant difference between the two treatment groups (Table 1).

Table 1. Progression-Free Survival for Subgroups Stratified According to Motzer Risk Score.

	Progression-Free Survival (Mos.)		
	Bevacizumab + Interferon	Interferon + Placebo	Hazard Ratio, P Value
Overall	10.2	5.4	0.63, <0.0001
Subgroups			
Favorable	12.9	7.6	0.60, 0.004
Intermediate	10.2	4.5	0.55, <0.0001
Poor	2.2	2.1	0.81, 0.457

At the time of interim analysis of overall survival, 251 of 450 scheduled events had occurred. The median overall survival had not been reached for the interferon plus bevacizumab arm and was 19.8 months for the interferon alone arm.

Interferon plus bevacizumab was well tolerated. The rate of grade 3 or 4 adverse events was 60% for the combination therapy arm and 45% for the interferon alone arm. The most common grade 3 or 4 adverse event was fatigue/asthenia/malaise, which occurred more frequently among patients who received interferon plus bevacizumab (23% vs 15%).

Prophylactic Cranial Irradiation in Extensive Disease Small Cell Lung Cancer

Percutaneous cranial irradiation (PCI) has had benefit for patients with limited disease small cell lung cancer (SCLC). The findings of a study now indicate that PCI also has benefit in the setting of extensive disease (ED)-SCLC, where the risk of brain metastases is high.

Ben Slotman, MD, PhD, VU University Medical Center, Amsterdam, the Netherlands, reported the findings of a study in which PCI led to a significant reduction in the risk of symptomatic brain metastases and a significant prolongation of survival.

The trial involved 286 patients with ED-SCLC who had a response to standard chemotherapy. The patients were randomly assigned to the PCI group (143 patients) or to the control group (143 patients). Persistent primary disease was present in approximately 75% of the patients in each group. Approximately 70% of patients had persistent metastases to lymph nodes, bone, lung, or other sites after completion of chemotherapy. Radiotherapy was usually given as 20 Gy in 5 fractions. Other radiotherapy schemes included 24-30 Gy in 8-12 fractions and 30 Gy in 10 fractions.

Dr. Slotman said that symptomatic brain metastases was defined as the radiographic evidence of brain metastases and the presence of one or more key symptoms. These symptoms included signs of increased intracranial pressure, headache, nausea and/or vomiting, cognitive and/or affective disturbances, seizures, or focal symptoms.

At 1 year, the rate of symptomatic brain metastases was significantly lower for patients in the PCI group than for patients in the control group (Table 1). One-year overall survival was also significantly better for patients treated with PCI. Dr. Slotman reported that PCI had no significant effect on extracranial disease progression. However, the treatment extended failure-free survival (Table 1). Symptomatic brain metastases was the first event in 9% of patients in the PCI group compared with 35% of patients in the control group.

Table 1. Comparison of Outcomes for PCI Group and Control Group.

	PCI Group (N = 143)	Control Group (N = 143)	Hazard Ratio, P Value
Rate of symptomatic brain metastases (%)	14.6	40.4	0.27 (0.16-0.44), <0.001
One-year overall survival rate (%)	27.1	13.3	0.68 (0.52-0.88), 0.003
One-year failure-free survival rate (%)	23.4	15.5	0.76 (0.59-0.96), 0.02