[News * Analysis * Commentary * Controversy]

SPECIAL EDITION supplement to
August 10, 2011 issue

Oncology Times

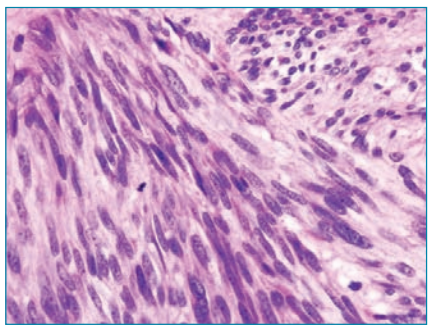
Publishing for 33 Years

Meeting Reporter

THE INDEPENDENT HEM/ONC NEWS SOURCE

American Society of Clinical Oncology 47th Annual Meeting

June 2011 • Chicago



Lippincott Williams & Wilkins
Wolters Kluwer Health

PERIODICALS

Plenary Session Highlights Two Practice-Changing Pediatric Trials: Survival Increases in High-Risk Neuroblastoma & ALL

BY RABIYA S. TUMA, PHD

The plenary session at the ASCO Annual Meeting regularly features practice-changing trials that are likely to be important to the entire cancer community. This year's program was no different, except that two of the trials reported survival improvements in pediatric cancers: neuroblastoma and acute lymphocytic leukemia (ALL).

"This is, I think, the first time there are two plenary pediatric presentations, showing important ways in which clinical trials can be conducted for orphan diseases," Lisa Diller, MD, Director of the Childhood Cancer Survivor Program at Dana-Farber Cancer Institute, said at a news conference prior to the plenary session. "And of interest, both of the trials use really old drugs."

Given the fact that the new ASCO president, Michael Link, MD, is a pediatric oncologist, *OT* asked whether the inclusion of two pediatric trials in the plenary session was a strategic move to help raise awareness amongst ASCO attendees about childhood cancers. Immediate Past-President George W. Sledge Jr., MD, answered quickly, saying, "The reality is we chose the plenary session abstracts based on what is the best science—all of which are practice changing, all of which improve survival."

iStockphoto.com/eva serrabassa

Dr. Link, the Lydia J. Lee Professor of Pediatric Hematology/Oncology at Stanford University School of Medicine, concurred with that statement, but acknowledged that he does want to increase the visibility of pediatric oncology: "I would like to raise the awareness of pediatrics in the community, but that was unrelated to these abstracts being selected."

He then laughed and added, "They would have gone better in my year, but then people probably would have said it was done because it was the year of the child. So I am actually glad it was done in George's year."

Pediatric oncology does appear to be an increasingly important part of the annual meeting, according to Eric C. Larsen, MD, Director of the Maine Children's Cancer Program and the Division of Pediatric Hematology/Oncology at the Barbara Bush Children's Hospital at Maine Medical Center, who presented the plenary abstract on high-risk ALL.

"Historically, it has not always been clear how worthwhile it was to attend ASCO as a pediatric hematologist/oncologist," he said in a phone interview. "I think that is definitely changing. There is a well-developed pediatric track, and there is more going on throughout the meeting. I don't have any data on this, but just informally talking to some of my colleagues around the country, ASCO is now an important meeting to attend."

Both the adult and pediatric oncology communities stand to benefit from regular, meaningful interaction, according to experts interviewed. But one area where pediatric oncology stands out is in clinical trial enrollment, with approximately 60% of US pediatric cancer patients participating in a trial.

"The amazing progress in ALL and other childhood tumors is a direct result of enrollment," Dr. Larsen said. "It is standard for children with cancer to be on a clinical trial when it is available. That happens more often than not."

By contrast, only 3% to 4% of adult cancer patients enroll in trials. "If it went to 10% in adults, though, it would crash the NCI budget for clinical trials," Dr. Sledge said, noting that the cooperative group budget is only about $250 million per year. "So we are limited in making progress in adults in large part because we have structural limitations built into federal funding."

High-Dose Methotrexate Better than Capizzi Methotrexate in High-Risk ALL

Children and young adults treated with high-dose methotrexate had nearly a 7% improvement in event-free survival compared with patients treated with escalating Capizzi methotrexate, according to a plenary report at the ASCO Annual Meeting. High-dose methotrexate also proved to be less toxic than the standard Capizzi method.

The outlook for children and young adults with acute lymphocytic leukemia (ALL) has been improving steadily for decades, with overall survival climbing from approximately 10% in the late 1960s to 75% to 85% now. About 10 years ago, however, pediatric oncologists noticed that an increasing proportion of patients suffered central nervous system relapse, as opposed to the more common bone marrow failures. With that in mind investigators looked around for drugs that could penetrate the CNS more efficiently, explained Eric C. Larsen, MD, Director of the Maine Children's Cancer Program and the Division of Pediatric Hematology/Oncology at the Barbara Bush Children's Hospital at

continued on page 17

ERIC LARSEN, MD, said that given the current results from the pediatric ALL trial, there has been a lot of discussion about whether the adult trial should be amended. "I think the question is whether they should continue what they are doing with Capizzi methotrexate, or perhaps it may be time to use high-dose methotrexate, certainly in the young adults, which I think many of us think that is the right way to go."

Choice of Myeloablative Regimen for Neuroblastoma Extends Survival in High-Risk Pediatric Patients

Long-term survival for high-risk neuroblastoma remains around 40%, despite intensive, multimodal treatment including myeloablative therapy and stem cell transplant. With few novel strategies on the horizon, pediatric oncologists have been making small, but significant gains by tweaking available regimens.

In the current study, reported during the plenary session, the International Society of Paediatric Oncology European Neuroblastoma Group (SIOPEN) compared two commonly used myeloablative regimens in pediatric high-risk neuroblastoma patients.

Patients treated with a combination of busulfan and melphalan (BuMel) had significantly increased event-free and overall survival compared with patients treated with a combination of carboplatin, etoposide, and melphalan (CEM). Additionally, patients treated with BuMel had fewer serious adverse events and intensive care unit admissions than those treated with CEM.

"These are the results of the trial, which we find quite extraordinary and

continued on page 17

RUTH LADENSTEIN, MD, MBA: "We found the results quite extraordinary and above our expectations, seeing a big advantage of 16% for BuMel in three-year event-three survival, This is the first time in pediatric oncology that we can clearly demonstrate that the choice of myeloablative therapy really matters. And the strongest benefit was in patients with residual disease, and we believe this is due to the ability of the drug to work on resting tumor cells."

→HIGH-RISK ALL

continued from page 16

Maine Medical Center in Portland, who presented the new study.

With no novel agents available, researchers in the Children's Oncology Group (COG), decided to try optimizing methotrexate.

"Methotrexate is a very important part of treatment for childhood ALL," Dr. Larsen said. "It is a key component of maintenance therapy, which is the longest phase of therapy, and over the years we have also tried ways of intensifying methotrexate therapy with the idea that more is better.

"We hoped and hypothesized that high-dose methotrexate would be better, because we were trying to increase our ability to control or prevent CNS relapse, and we know that high-dose methotrexate probably penetrates the CNS better. Interestingly, with the results we have so far, high-dose methotrexate clearly decreases the chance of CNS relapse, which makes sense, but it also seems to decrease the chance of bone marrow relapses as well—and that seemed to be fairly significant."

Clear Victor

Prior studies suggested that high-dose methotrexate might be better for CNS control than the Capizzi method, but the two treatments had not been tested head-to-head. To answer the question, COG investigators enrolled more than 3,000 patients in a Phase III trial in which patients were treated with either high-dose methotrexate or Capizzi methotrexate during maintenance therapy (*see box for regimen details*).

The median five-year event-free survival for 1,209 patients evaluable in the high-dose methotrexate arm was 82.0%, compared with 75.4% for 1,217 patients evaluable in the Capizzi arm.

Patients who were initially slow to respond to treatment appeared to derive the greatest benefit from the high-dose therapy with a five-year event-free survival of 79.5% (n=202), compared with 65.4% for the slow responders in the Capizzi arm (n=233).

As Dr. Larsen noted, there was a reduction in isolated CNS relapses, as hypothesized, as well as a reduction in the rate of marrow relapses in patients treated with high-dose methotrexate, compared with the Capizzi regimen. Specifically, the rates of isolated CNS relapse in the two arms were 1.8% and 2.6%, respectively, while the rates of marrow failure were 3.5% and 5.6%, respectively.

Although there was some concern prior to starting the trial that the high-dose methotrexate might increase serious adverse events, it proved to be less toxic. The rates of Grade 3+ toxicities were similar in the two arms, except for febrile neutropenia, which occurred in 5.2% of the patients treated on the high-dose arm and in 8.2% of those treated in the Capizzi arm.

> Prior studies had suggested that high-dose methotrexate might be better for CNS control than the Capizzi method, but the two treatments had not been tested head-to-head.

"High-dose methotrexate was substantially better," noted ASCO President Michael Link, MD. "Here is a group of patients without a particular [molecular] target available that we can employ, and yet we can still make progress and improve the outcome for patients."

Potential Impact on Adult ALL Therapy

Recent data suggest that young adult patients who are treated on pediatric trials do better than those treated as adults. What has not been clear, though, is whether the difference is due to a difference in disease biology; treatment regimens; which tend to be more intense in pediatric care; or some other unknown variable in care.

To start to answer that question, adult oncologists in Cancer and Leukemia Group B decided to adopt one arm of the COG trial to see if they could obtain equivalent benefits. The adult oncology group opted for the Capizzi arm, which they opened in 2007.

Given these current results from the pediatric trial, Dr. Larsen said that there was now a lot of discussion about whether the adult trial should be amended. "I think the question is whether they should continue what they are doing with Capizzi methotrexate, or perhaps it may be time to use high-dose methotrexate, certainly in the young adults," Dr. Larsen said. "I think many of us think that is the right way to go."

COG Trial AALL0232 Interim Maintenance Regimen

Capizzi Methotrexate

- MTX 100 mg/m^2 on Days 1, 11, 21, 31, and 41
  No Rescue
  Each Dose Increased by 50 mg/m^2
- PEG Asparaginase on Days 2 and 22
- Intrathecal MTX on Days 1 and 31
- Vincristine on Days 1, 11, 21, 31, and 41

High-Dose Methotrexate

- MTX 5 gm/m^2 on Days 1, 15, 29, and 43
- Leucovorin Rescue
- 6-Mercaptopurine Orally on Days 1-56
- Intrathecal MTX on Days 1 and 31
- Vincristine on Days 1, 15, 29, and 43

→NEUROBLASTOMA

continued from page 16

above our expectations, seeing a big advantage of 16% for BuMel in three-year event-three survival," said Ruth Ladenstein, MD, MBA, Associate Professor of Pediatrics at the University of Vienna and St. Anna Children's Cancer Research Institute in Vienna, who presented the trial data.

A total of 583 patients with high-risk neuroblastoma enrolled in the trial from 20 countries between 2002 and 2010. Patients received a complex treatment regimen, including induction therapy with rapid COJEC (cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide given in a rapid delivery schedule), followed by stem cell harvest, surgery, myeloablative therapy with either BuMel or CEM, stem cell rescue, radiotherapy for local control, and maintenance therapy (*see box for BuMel and CEM details*).

With a median follow-up of 3.5 years, patients treated in the BuMel arm had a three-year event-free survival rate of 49% compared with 33% for the patients treated in the CEM arm. Three-year overall survival was also higher in the BuMel arm at 60% compared with the CEM arm at 48%.

"Most interestingly, this was really related to a decreased relapsed rate in the BuMel regimen and was not related to transplant related mortality, which was four to six percent in both regimens," Dr. Ladenstein said.

The most common Grade 3/4 toxicity in patients treated with BuMel was veno-occlusive disease, which occurred in 5% of patients compared with 1% of the patients in the CEM arm. By contrast, Grade 3/4 infections, fever, stomatitis, nausea/vomiting, and renal toxicity were more common in the CEM arm (specific percentages were not provided).

"This is the first time in pediatric oncology that we can clearly demonstrate that the choice of myeloablative therapy really matters," Dr. Ladenstein said. "BuMel is superior to CEM in high-risk neuroblastoma in both event-free and overall survival. And the strongest benefit was in patients with residual disease, and we believe this is due to the ability of the drug to work on resting tumor cells."

BuMel vs CEM

BuMel:

- Busulfan (oral; before 2006); 4x150 mg/m^2 in 4 equal doses.
- Busilvex (intravenous, after 2006), according to body weight.
- Melphalan 140 mg/ m^2/day.)

CEM:

- Carboplatin continuous infusion, 4x AUC 4.1 mg/ml/min/day.
- Etoposide continuous infusion, 4x 338 mg/m^2/day or 4x 200 mg/m^2/day.
- Melphalan 3x 70 mg/m^2/day or 3x 60 mg/m^2/day

A Question of Treatment Interaction?

The Discussant for the study, Julie R. Park, MD, Chair of the Neuroblastoma Scientific Committee of the Children's Oncology Group and Associate Professor of Pediatrics at the University of Washington, agreed that the new data demonstrate that BuMel is the more effective myeloablative therapy within the context of the overall regimen used by the European researchers.

However, looking at the event-free survival rate of the patients treated with CEM in this trial, she said it appeared to be considerably lower than what has been seen in recent COG trials. One reason for this difference may be the other parts of the treatment regimen, including the type of induction therapy used. In this trial, the researchers opted for rapid COJEC, whereas the US-based COG trails used the modified Memorial Sloan-Kettering N6 induction regimen.

Therefore, while Dr. Ladenstein concluded that BuMel should be the new standard of care for myeloablative therapy in high-risk neuroblastoma patients, Dr. Park made a more modest statement saying that it was superior within the context of patient treated with rapid COJEC induction therapy.

continued on page 18

ALK-Positive NSCLC: Crizotinib Extends Survival, Called New Standard of Care

BY ROBERT H. CARLSON

"Crizotinib is an oral compound that inhibits the therapeutic target of ALK as well as c-MET, a mesenchymal-epithelial transition factor."

CHICAGO—ALK (anaplastic lymphoma kinase) represents one of the newest tyrosine kinase targets in lung cancer. A Phase I trial reported last fall (*Kwak et al: NEJM 2010;363-1693-1703*) showed that the ALK tyrosine kinase inhibitor crizotinib had significant antitumor activity in patients with advanced ALK-positive non-small-cell lung cancer (NSCLC), but any impact on overall survival was not established.

Now, data from an expansion cohort of that trial reported in an oral session at the ASCO Annual Meeting show that crizotinib therapy is indeed associated with a longer overall survival compared with ALK-negative patients and with ALK-positive patients not treated with crizotinib (*Abstract 7507*).

"Crizotinib may prolong overall survival and fundamentally alter the natural history of ALK-positive NSCLC," said lead author Alice T. Shaw, MD, PhD, attending physician in the Thoracic Cancer Program at Massachusetts General Hospital and Assistant Professor of Medicine at Harvard Medical School. She and her co-researchers proposed in their abstract that crizotinib represents a new standard of care for patients with ALK-positive NSCLC.

The study reported by ALICE T. SHAW, MD, PHD, found that ALK-positive patients treated with crizotinib had a two-year survival rate of 54% compared with 33% for ALK-positive controls. A randomized, controlled trial is now under way to confirm the survival outcomes.

In her presentation, Dr. Shaw explained that crizotinib is an oral compound that inhibits the therapeutic target of ALK as well as c-MET, a mesenchymal-epithelial transition factor.

The expansion cohort trial, which was sponsored by Pfizer, included 82 ALK-positive patients. For comparators, 36 ALK-positive patients who were not treated with crizotinib were chosen from other Phase I sites, as well as 253 ALK-negative and EGFR-negative patients from one site. All ALK-positive and ALK-negative controls had advanced NSCLC.

ALK-positive patients treated with crizotinib had a one-year overall survival rate of 74% and a two-year overall survival rate of 54%. Median overall survival had

continued on page 19

→NEUROBLASTOMA

continued from page 17

Breaking the 'Magical' 50% Threshold

That said, both Dr. Park and ASCO President Michael Link, MD, commended the SIOPEN researchers for their commitment to the trial, which took more than eight years to accrue.

Dr. Link noted that pediatric oncology trials are challenging at the moment because researchers are not particularly interested in response rates and events don't occur quickly in many pediatric cancers—a fact he said he is thankful for—which mean the trials take a long time.

"We need to have some out-of-the-box thinking in terms of how to design trials so that we get answers more quickly," he said. "At the current speed, by the time we are in the middle of accrual for one trial, a better idea is already emerging. So there is a kind of anxiety about getting to the end of a trial, so we can get to a new or more exciting treatment.

"I don't think it is a trivial question, but even with international collaboration, we're limited by the numbers of patients available and the endpoints we're looking for."

"We need out-of-the-box thinking about how to design trials so that we get answers more quickly. At the current speed, by the time we are in the middle of accrual for one trial, a better idea is already emerging. So there is a kind of anxiety about getting to the end of a trial, so we can get to a new or more exciting treatment. I don't think it is a trivial question, but even with international collaboration, we're limited by the numbers of patients available and the endpoints we're looking for."

—Michael Link, MD

In the end though, Dr. Ladenstein says that the past two years have really been watershed ones for neuroblastoma. During last year's ASCO Annual Meeting, investigators presented evidence that the addition of immunotherapy, with the use of the mAb 14.18 antibody, to the maintenance phase of treatment might increase overall survival by 20% in patients with a strong remission and 10% in the population as a whole.

Adding those gains to the ones she described at the 2011 ASCO meeting, Dr. Ladenstein said, "One may speculate that these two years have garnered a potential of 20 to 30 percent better event-free and overall survival in high-risk neuroblastoma. This is quite a breakthrough that I want to underline.

"We are really moving above 50% in long-term outcome, which was like a magic threshold that we have never really reached before in the complete patient cohort."