Trends-in-Medicine

September 2005
by D. Woods

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA Oncologic Drugs Advisory Committee Recommends Approval of Arranon to Treat Leukemia and Lymphoma

Bethesda, MD
September 14, 2005

The FDA's Oncologic Drugs Advisory Committee (ODAC) unanimously voted to recommend accelerated approval for GlaxoSmithKline's injectable leukemia and lymphoma drug Arranon (nelarabine) for adult patients, and voted 11-1 in favor of the drug's use in children.

Glaxo is seeking approval to market Arranon to patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. The drug has received orphan designation from the FDA.

T-ALL is a rare, hard-to-treat version of the disease, a type of blood and bone marrow cancer in which too many white blood cells are made. In T-LBL, a more serious type of non-Hodgkin's lymphoma, cancer attacks the immune system's lymph nodes. Arranon is a soluble pro-drug of Ara-G, which mimics PNP deficiency state and targets T-cells for selective destruction.

The Company Perspective

The company said that Arranon has demonstrated:

- Pharmacological selectivity for T-cells.
- Clinical efficacy in children and adults and in relapsed and refractory disease.
- Well-characterized safety profile.
- Favorable risk:benefit profile in heavily pre-treated patients.

A company speaker said that the drug meets a significant unmet medical need, as there is no proven effective alternative therapy available for T-ALL and T-LBL.

T-ALL and T-LBL are rare diseases, with only about 1,600 new cases a year. The two diseases differ only by the percentage of lymphoblast in the bone marrow. Most victims are older children and young adults. Current treatment is multi-agent chemotherapy at time of diagnosis and at first relapse. Every year, about 500 patients have a relapse. A company official said that conventional first-line treatment is insufficient for one child in three. The speaker said, "What our patients clearly need are new drugs…to both give remissions and meaningful durations of remissions – long enough to get a stem cell transplant."

Another company speaker described the company's two trials of the drug. The primary endpoint was conventionally-defined remission in bone marrow and hemograms. Less than 5% of lymphoblasts were required. A speaker said that the survival rate was very encouraging and pointed out that there were consistent rates of remission for adult and pediatric patients and for patients with relapsed and refractory disease across the Phase I and II studies.

The Glaxo safety presenter said that 980 patients have received Arranon, with 459 patients in a full safety database. He said that hematologic events were the most common adverse events, and he described them as "manageable." Neurologic events were common, mostly Grade 1 or 2, with 13% Grade 3 or 4 for adults, and 19% Grade 3 or 4 for pediatrics. There were fatal adverse events related to the drug in 1% of patients. He concluded that the recommended doses have acceptable risk.

Nine out of 187 patients (5%) died – 6 of 103 adults and 3 of 84 children – due to adverse events at the proposed doses. Two deaths (1%) were attributed to Arranon: coma and status epilepticus.

Pediatric: COG-P9673
Response Rate and Duration ≥2 Prior Inductions (n=39)

Response	CR	CR + CR*
Response Rate	13%	23%
Median Duration of Response	9 weeks	9 weeks
Duration of Response	5 – 36 weeks	3 – 42 weeks

Efficacy Summary ≥2 Prior Multi-Agent Inductions

Measurement	Adult trial CALGB-19801	Pediatric trial COG-P9673
CR + CR*	21%	23%
Duration of CR + CR*	4 - 195+ weeks	3 - 42 weeks
Median overall survival	21 weeks	13 weeks
1-year survival	29%	14%

Response Rate in Supportive Trials of Patients with Relapsed/Refractory T-ALL/T-LBL

Age group	Study	Number of patients	CR
Adult	TRC 9701 Special Exceptions (University of Frankfurt)	24 16	13% 56%
Adult	PGAA1001 PGAA1002 PGAA1003	14 3 8	29% 0 0
Pediatric	PGAA1001 PGAA1002 PGAA1003	18 5 2	33% 40% 50%
TOTAL		**90**	

Adult: CALGB-19801 Response Rate and Duration ≥2 Prior Inductions (n=28)

Response	CR Complete response with full hematologic recovery	CR + CR* Best response either with or without full hematologic recovery
Response rate	18%	21%
Median duration of response	29 weeks	24 weeks
Duration of response	15 - 195+ weeks	4 - 195+ weeks

The FDA Perspective

The FDA staff said that the drug shows efficacy and is generally safe:

- Principal toxicities in pediatric patients were laboratory abnormalities.
- Principal toxicities in adult patients were hematologic, gastrointestinal, fever, fatigue, and respiratory.
- Neurologic toxicity was dose limiting. Most neurologic toxicity resolved over time.

An FDA speaker said that data showed nelarabine activity against T-cells. He said, "Because stem cell transplant may be associated with remission, there is pressure to proceed with transplant if a suitable donor is available."

The FDA staff divided the patients into groups:

- **Group 1** – T-ALL or T-LBL in first relapse with or without concomitant extramedullary relapse – other than CNS. For pediatric patients, the longest remission duration was about nine weeks. For adult patients, the longest remission duration was 195+ weeks.
- **Group 2** – T-ALL or T-LBL in second or later relapse with or without concomitant extramedullary relapse – other than CNS. For pediatric patients, the longest remission duration was about 14 weeks. For adult patients, the longest remission duration was 217 weeks.

In supportive Phase I trials made up of three studies (pediatric and adult patients), the most common Grade 3/4 non-neurologic adverse events in the pediatric population were hematologic (~90%). An FDA official said that a confounding factor in the studies were that some patients were transplanted during the study, making it uncertain how much transplanted-related treatment and nelarabine contributed to patients' remissions.

Adverse Events in Phase I Trials

Grade 3/4 adverse event	Pediatric	Adult
Infections	3%	9%
Increased transaminases	4%	2%
Increased bilirubin	9%	---
Decreased albumin	6%	---
Decreased potassium	6%	---
Asthenia	1%	1%
GI	---	3%
Fatigue	---	12%
Respiratory disorders	---	10%

Transplant outcomes

The company was asked about the outcome of transplants. A Glaxo speaker responded that, out of six adult responders, two patients had a transplant, "We can see there were patients who had a prolonged survival without transplant. So, trying to differentiate in this setting, we can just make gross comparisons to see if transplant itself was an overriding factor in survival. In this limited population it was not. In pediatrics, there were more patients with transplants – four – and, in and of itself, transplant does not seem to be a factor for overriding survival…We agree with FDA that transplant can be a confounding issue with regard to treatment of this disease. We looked at 15 patients who achieved a response CR + CR*. The response duration is from the time of an initial response – which for patients with ALL could be marrow complete response and for the LBL could be from the time of complete remission – until the time of a next event, with that event being transplant, relapse, coming off the drug because of any other event. Some patients have short duration in response, but that is because transplant is the next step…In a second group of patients who had a relapse, all of the patients had a duration of remission of 10 weeks or longer (up to 195+ weeks). Five patients had duration of <8 weeks before a relapse."

Toxicity

An oncologist/hematologist on the panel asked, "They (Glaxo) have conducted another study with nelarabine in non-Hodgkin's lymphoma, and that trial was shut down because of toxicity. Do you know why?" A Glaxo official responded, "From our experience in the leukemia community, we did not see concerning neurotoxicity. Whether it's related to age or prior therapies, those might be reasons, but in young adults we did not see worrisome toxicity in our Phase II trial."

FDA Questions to the Panel and Panel Votes

Question 1: *In pediatric patients with ≥2 prior inductions, 9 of 39 (23%) of patients had CR [with full hematologic recovery] or CR* [without hematologic recovery]. Four of 9 CR or CR* patients who did not have their CR or CR* duration confounded by subsequent transplant or other systemic chemotherapy had CR or CR* durations of 3.3, 3.6, 6.1, and 9.3 weeks. Are these results reasonably likely to predict clinical benefit in this setting?*
YES by a vote of 11 to 1

Panel member (biostatistician): "In the bottom line, it seems as if the response is giving you at very best two extra months in a quarter of the patients, and that translates to two weeks in every patient, and that's probably an over-estimate…In the pediatric part it seems so short. It's less impressive than other agents in the literature."

Panel member (hematologist/oncologist): "These are exceptionally difficult patients with no options, and hospice or experimental drug is it. There's nothing for these patients. Transplant is the best option if you can get them there. I know nothing out there that has as much promise as this now…The goal would be to identify the patients earlier in the disease."

Panel member (hematologist/oncologist): "These patients are facing death. You have to put them into a CR in order to get them to a transplant, and this gets a person into a CR long enough to get a transplant. This is a drug that's worth approval."

FDA: "This is not the first drug we've talked about in a refractory setting where we talk about minor response rates. Some have been winners."

Question 2: *In adult patients with ≥2 prior inductions, 6 of 28 (21%) patients had CR or CR*. Five of 6 CR or CR* patients who did not have their CR or CR* duration confounded by subsequent transplant or other systemic chemotherapy had CR or CR* durations of 4, 15, 19, 30, and 195+ weeks. Are these results reasonably likely to predict clinical benefit in this setting?* **Unanimously YES**

A biostatistician on the panel commented, "The data is much more favorable here, so reasonably likely I would say yes."

Question 3: *Is the risk:benefit ratio favorable?* **No vote**

Question 4: *Should this NDA be granted accelerated approval for:*

a. *Adults?* **Unanimously YES**

b. *Pediatric population?* **YES by a vote of 11 to 1**

♦