Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Working Group Conference Call
August 5, 2014
11:00 a.m.–11:50 a.m. ET

Participants

Amy Barone, M.D.
Susan Blaney, M.D.
Denise Casey, M.D.
Meredith Chuk, M.D.
Martha Donoghue, M.D.
Mark Kieran, M.D., Ph.D.
Gregory H. Reaman, M.D.
C. Patrick Reynolds, M.D., Ph.D.
Malcolm Smith, M.D., Ph.D.
Donna Snyder, M.D.
Perdita Taylor-Zapata, M.D.
Brenda Weigel, M.D., M.Sc.
James Whitlock, M.D.
Erica Wynn, M.D.
Anne Zajicek, M.D., Pharm.D.

Purpose

The purpose of this call was to discuss the following:

- Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) meeting scheduled for December 11–12, 2014
- Tentative list of products:
  - Ganetespib (STA 9090)
  - NKTR-102 (etirinotecan pegol)
  - R06839921
- Other products of potential interest: Lymphoseek (technetium Tc 99m tilmanocept)
- Plans for a mini-workshop/symposium: Master (basket/umbrella) protocol considerations in pediatric oncology
- Dexrazoxane and pediatric use: potential off-patent Written Request (WR) opportunity.

Pediatric Subcommittee of the ODAC Meeting and Tentative List of Products

Dr. Reaman announced that the Pediatric Subcommittee of the ODAC meeting is scheduled for December 11–12, 2014. The subcommittee will tentatively discuss the following three products.

Ganetespib. Ganetespib is a synthetic small-molecule heat shock protein 90 (Hsp90) inhibitor. Dr. Reaman said that the drug's manufacturer, Synta, has tentatively agreed to present at the meeting. Ganetespib is being evaluated in adults with a variety of soft tissue sarcomas.

NKTR-102. NKTR-102 is a novel agent that has some interesting pharmacologic properties (longer AUCs and somewhat diminished toxicity because of lower peak concentrations). There are a number of adult cancer indications for which this drug is being studied. The drug's manufacturer (Nektar) is interested in potential pediatric development. Given irenotecan's widespread and unapproved use, NKTR-102 might be a reasonable product to discuss. Nektar has confirmed they will present at the Pediatric Subcommittee meeting.

R06839921. This drug is an MDM2 inhibitor. The drug's manufacturer (Hoffmann-LaRoche/Genentech) indicated that it wants to discuss R06839921 at one of the Pediatric Subcommittee meetings. Hoffmann-LaRoche/Genentech is interested in learning about how this drug might be developed for pediatrics. They have a Center for Excellence in Pediatrics, specifically pediatric oncology. They have approached the FDA with a request to accommodate early discussion of promising pipeline agents. R06839921 is one of a series of Hoffmann-LaRoche/Genentech drugs that will potentially be included in future Pediatric Subcommittee meeting agendas.

Other potential products. Dr. Reaman noted that Bristol-Myers Squibb has an expanding immuno-oncology drug pipeline. The Pediatric Oncology Working Group previously discussed two of their products—ipilimumab and nivolumab—and possible WRs for these drugs. He asked the call participants whether there are other compounds for potential pediatric development that the subcommittee could solicit the sponsor to present at a Pediatric Subcommittee meeting. Dr. Reaman said Dr. Ron Portman would like to have a small meeting with investigators, representatives from the National Cancer Institute (NCI), and representatives from the U.S. Food and Drug Administration (FDA) to discuss other potential agents as well.

Dr. Whitlock noted that blinatumomab has applied for accelerated approval for use in adults. Its path for pediatric development is fairly well established and probably does not need further consideration by the Pediatric Oncology Working Group. Inotuzumab ozogamycin is a promising drug for pediatric acute lymphoblastic leukemia. Dr. Whitlock and European colleagues have been working with Pfizer to resubmit a Pediatric Investigation Plan (PIP) proposal. Once they know how the PIP is received, inotuzumab could be discussed by the working group as a candidate for discussion at a Pediatric Subcommittee meeting.

Other Products of Potential Interest: Lymphoseek

Dr. Reaman said that Lymphoseek is an imaging agent, not a therapeutic agent. ODAC became aware of Lymphoseek during consults because of its intended use in lymphoid mapping in a variety of cancers, notably breast cancer, as well as head and neck cancer and melanoma.

Dr. Donoghue explained that Lymphoseek is a radioactive diagnostic agent indicated for sentinel lymph node detection and excision for breast cancer and melanoma and for lymphatic mapping.

Lymphoseek was recently approved for squamous cell carcinoma of the head and neck. The Division of Medical Imaging Products sought an opinion as to whether studies of Lymphoseek would be beneficial in pediatric patients. The company (Navidea) was not seeking pediatric studies primarily because of the lack of consensus on the role of lymphatic mapping for a variety of solid tumors. The patient population may be too small, and there may not be enough investigator interest to consider a study. The Office of Hematology and Oncology Products is considering inviting Navidea to explore potential pediatric studies at a Pediatric Subcommittee meeting.

Dr. Reaman commented that if Lymphoseek seeks a broader indication it might trigger a pediatric evaluation as required by the Pediatric Research Equity Act. There should be broader consultation and input before suggesting to Navidea whether pediatric evaluation is warranted. Based on the surgical guidelines for pediatric rhabdomyosarcoma and neuroblastoma, a clinical trial of Lymphoseek could be considered and a potential pediatric trial could be discussed by the Pediatric Subcommittee if there are appropriate experts representing pediatric surgery, solid tumor oncology, and imaging. Dr. Reaman asked the working group to provide input on pediatric surgeons and medical imaging experts to include in possible discussions of Lymphoseek, if put on the agenda for a future ODAC meeting.

Plans for a Mini-Workshop/Symposium: Master Protocol Considerations in Pediatric Oncology

Dr. Reaman said master protocols in pediatric oncology will be tentatively discussed at a mini-workshop/symposium on September 11, 2014. Medical oncologists have an intense interest in this topic. Dr. Reaman noted the NCI-MATCH study as one example. There is also a lung cancer master protocol in squamous non-small cell lung cancer using next-gen sequencing to identify potential agents to which patients are allocated. This protocol is a multi-drug, multi-sponsor collaboration. There are many issues and challenges regarding the use of master protocols, and this is especially true in potential pediatric oncology trials. The mini-workshop will be small and is envisioned to be information-gathering for the FDA to be apprised of current plans and address regulatory considerations to facilitate the process of developing pediatric master protocols. Those interested in the mini-workshop may be able to participate via teleconference.

Dexrazoxane and Pediatric Use: Potential Off-Patent WR Opportunity

Dr. Reaman explained that dexrazoxane is used as a cardioprotective agent and is not approved for use in children in the United States. The drug is contraindicated for children in Europe. WRs were issued many years ago to Pharmacia and Upjohn and later to Pfizer, which were refused. Dr. Reaman asked whether there is an opportunity for an off-patent WR for dexrazoxane and whether it should be explored. Dr. Zajicek said there were discussions several years ago. Given the drug's widespread use in the pediatric population, information to inform labeling is worth considering. Drs. Zajicek, Smith, and Reaman agreed to discuss the off-patent WR for dexrazoxane after the working group's conference call.

Other Topics

Dr. Kieran reported that several years ago a phase 1 clinical trial was conducted with Xerecept, which is a steroid-sparing synthetic corticotropin-releasing factor. The compound was administered to terminal-phase children with diffuse intrinsic pontine glioma to get them off steroids due to the side effects. The trial was a dose-escalation study. For most of the children, the dosage of steroids was dramatically reduced during disease progression. Half of the children were able to discontinue steroids completely. The phase 1 trial was successful in determining dose. Although the drug is not therapeutic, it improves a patient's quality of life. The drug has not been approved because the FDA has not determined whether reducing or discontinuing steroids are sufficient criteria for approving the drug. The FDA would not accept the Palliative Care Quality of Life Instrument as a sufficient measure of the children getting better because they could not objectively evaluate patient-reported outcomes, such as fatigue and tiredness, as endpoints.

Dr. Kieran asked whether there is some appropriate mechanism for exploring the approval of drugs such as Xerecept, which are focused on reducing side effects and not on therapeutics. Dr. Reaman said the BPCA program may not be the appropriate mechanism. A discussion by the Pediatric Subcommittee at an ODAC meeting might be appropriate and could be considered. Dr. Reaman suggested that the sponsor contact the Study Endpoints and Labeling Development (SEALD) Team and inquire about the Clinical Outcome Assessment Qualification Program.

Action Items:

- The Pediatric Oncology Working Group will provide input on pediatric surgeons and medical imaging experts to include in discussions of Lymphoseek.
- Drs. Zajicek, Smith, and Reaman will discuss the off-patent WR for dexrazoxane after the working group's conference call.
- Dr. Reaman will identify the people in the endpoint qualification program within the FDA's Office of Translational Science and provide the names to Dr. Kieran.
- Dr. Reaman will confirm the list of products to be discussed by the Pediatric Subcommittee at the December ODAC meeting.