

ONCOLOGIC DRUGS ADVISORY COMMITTEE PEDIATRIC SUBCOMMITTEE QUESTIONS

November 28, 2001
Holiday Inn, Gaithersburg, MD

The purpose of this meeting is to provide advice to the FDA on the implementation of the Pediatric Rule of 1998 with regard to study type and design if a pediatric indication is considered to be the same indication as an adult malignancy. The Pediatric Rule of 1998 (<http://www.fda.gov/ohrms/dockets/98fr/120298c.txt>) states that there is a Federal mandate to perform pediatric studies if the indication under review for a marketing license exists in children and if it represents a therapeutic advance or there will be substantial use (> 50 000 children) of the product. If the indication under review is not found in children or the product does not represent a therapeutic advance and less than 50 000 children would use it, then the requirement is waived. Fortunately, pediatric cancer is sufficiently rare that the substantial use trigger does not apply. The conditions that would trigger the Pediatric Rule are if the indication under review is found in children and the product represents a therapeutic advance.

Previous discussions about the application of the Pediatric Rule of 1998 to oncology outlined some principles and examples where an adult and pediatric condition may be considered the same indication. For the following questions, consider that such a determination has been made and implementation is being discussed.

Questions

A common approach for selecting starting dose for Phase I studies in children with cancer of cytotoxic therapies is to begin with 80% of the adult maximally tolerated dose (MTD). Children who currently enter Phase I studies tend to be more heavily pre-treated with other therapies than previously. In addition, many newer therapies are not cytotoxic in the manner that previously developed therapies were, and have different modes of action including modulation of cellular signaling pathways.

1. If a potential therapy has an established dose in adults based on the optimal biologically effective dose (OBD), what principles should be applied to designing studies in children? For example, should the starting dose be a percentage of the adult dose? Should the same exposure or AUC be targeted? What role should pre-clinical data play in study design?
2. If tumors that are considered to represent the same disease or condition are found in two different populations and/or share a common biological mechanism that is supported by a body of scientific evidence that is generally accepted and a therapy targets that mechanism, what types of studies would validate extrapolation of efficacy findings from one population to the other? Product labeling to support a marketing claim usually is dependent upon demonstration of patient benefit and an assessment that it is safe and effective for the intended use. If activity is noted in adults and the same tumor type, based on generally accepted criteria such as histology, cytogenetics, common biological mechanisms, etc., exists in children, what evidence would be needed to establish efficacy for product labeling (to make a marketing claim) for children with cancer?
3. If a therapy is intended to be used as part of a combination, are monotherapy studies in children advisable? If so, what types of studies should be implemented prior to initiating combination studies?

The Phase II window design exposes patients with a disease to a new therapy for a predefined limited period of time (the "window") prior to receiving standard therapy. This approach has been applied in settings where patients have a disease that is unlikely to enter long term remission. The rationale is that because patients in standard Phase I or Phase II studies have received extensive prior therapy, that the disease may not be representative of de novo disease, and that the patient may have compromised organ function. These factors may mask potential activity of a new therapy and may limit the ability to tolerate a new therapy. Administration of a new drug or biological at diagnosis may allow a better evaluation of the activity and therapeutic potential

What circumstances (for example, type of disease, expected results with available therapy, prognosis, types of patients) would warrant a phase II window design?