NDA 20-509_S033/2004_10_26

Gemcitabine Pediatric Exclusivity

Executive Summary

The effectiveness of Gemzar® (gemcitabine HCl) in pediatric patients has not been demonstrated.

Gemcitabine was initially evaluated in a Phase 1 dose finding study. The primary study endpoint was maximum tolerated dose (MTD). The secondary endpoint was pharmacokinetics, with measurement of gemcitabine blood concentrations, clearance, and distribution in body compartments. In this study fourteen heavily pretreated, refractory patients were enrolled, all with pediatric acute leukemia. The age range of study patients included infants 1 year of age to 20 years of age. Demographic and disease characteristics of study patients are summarized in Table 1. One of 6 patients receiving gemcitabine 10 mg/m^2/minute continuous infusion for 360 minutes weekly for 3 weeks had dose-limiting hematologic toxicity. Eight patients then received gemcitabine 10 mg/m^2/minute for 480 minutes. Three had dose-limiting toxicity. Thus the MTD is 10 mg/m^2/minute continuous infusion for 360 minutes weekly for 3 weeks with a one week rest. Eleven patients had pharmacokinetic studies done.

The phase 2 pediatric study performed by the Childrens Oncology Group, enrolled 20 evaluable patients with acute lymphoblastic leukemia (ALL) and 10 evaluable patients with acute myelogenous leukemia (AML). There were no patients with non-Hodgkin's lymphoma. The age range of study patients included infants 1 year of age to adolescents age $\leq$ 20. Demographic and disease characteristics of study patients are summarized in Table 2. Patients received gemcitabine 10 mg/m^2/minute continuous infusion for 360 minutes weekly for 3 weeks with a one week rest. The primary study endpoint was complete response (CR) rate. There was 1 CR (ALL). As in the phase 1 study, hematologic toxicity was dose-limiting. Other observed gemcitabine toxicities included febrile neutropenia, elevation of serum transaminases, nausea, vomiting and rash/desquamation. This toxicity spectrum was similar to that reported in adults.

The conclusion of the phase 2 study was that gemcitabine at the dose and schedule studied was not effective for children with relapsed ALL or AML. Appropriate sections of the label incorporate the findings of the above studies.

Pediatric exclusivity was granted in January 27, 2005.

Table 1. Characteristics of Eligible Children with Relapsed Acute Leukemia Enrolled on CCG 0955 Study

Characteristics	Value (N = 14)
Age at Study Entry (years) Median (Range)	9 (1 - 16)
Gender Male Female	 6 (43%) 8 (57%)
Race White Hispanic Asian	 5 (36%) 8 (57%) 1 (7%)
Histology ALL AML	 7 (50%) 7 (50%)
Gemcitabine dose 3600 4800	 6 (43%) 8 (57%)
Prior chemotherapy Yes	14 (100%)
Prior transplant Yes No	 3 (21%) 11(79%)
Prior radiation Yes No	 6 (43%) 8 (57%)

Table 2. Characteristics of Eligible Children with Relapsed Acute Lymphoblastic Leukemia or Acute Myelogenous Leukemia Enrolled on ADVLO22 Study

Characteristics	Value (N = 32)
Age at Study Entry (years) Median (Range)	10 (1 - 20)
Gender Male Female	 23 (72%) 9 (28%)
Race White Hispanic Black Asian	 18 (56%) 10 (32%) 2 (6%) 2 (6%)
Number of Chemotherapy Regimens Received Prior to Enrollment 1 2 3 4 6	 5 (16%) 12 (38%) 9 (28%) 4 (12%) 2 (6%)
Was Radiation Therapy Received Prior to Enrollment Yes No	 12(37%) 20 (63%)
Did the Patient Have a Bone Marrow Transplant Prior to Enrollment Yes No	 8 (25%) 24 (75%)

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