Phase II and pharmacokinetic study of GL331 in previously treated Chinese gastric cancer patients

Abstract Purpose: A phase II and pharmacokinetic study was designed to assess the efficacy and toxicity profile of an epidophyllotoxin analogue, GL331, in previously treated Chinese gastric cancer patients, with concurrent pharmacokinetic evaluation of the drug’s metabolism. Material and methods: GL331 was given at 200 mg/m² as a daily 3-h infusion for 5 days every 4 weeks. Results: Enrolled in the study were 15 patients. One patient died from neutropenic sepsis before evaluation, one patient did not receive the full dose for reasons unrelated to GL331, nine patients had progressive disease with a median survival of 80 days, and five had stable disease with a median survival of 240 days. Grade 3 and 4 myelosuppression occurred in 10 of the 15 patients, with one death from neutropenic sepsis. This patient’s peak GL331 concentration was 16.8 µg/ml, which was high compared to the mean peak drug concentration of 6 ± 4.1 µg/ml. The mean systemic GL331 clearance was 12.1 ± 7.2 l/h per m², much lower than 23.3 ± 8.2 l/h per m² found in the phase I trial. Topoisomerase IIα was determined by immunohistochemistry and overexpression was detected in 3 of 11 specimens. Conclusions: GL331 was ineffective at this dose and schedule in this group of patients in spite of adequate blood levels of the drug.

Keywords GL331 • Chinese • Refractory • Gastric cancer • Topoisomerase IIα

Introduction

Gastric cancer ranks as the sixth most common cancer in Taiwan with an incidence of 18.7/100,000, and 3093 new cases in 1996 were reported [6]. These figures are high compared to the USA incidence rate of 6.7/1000,000 in the same year [15]. The high local occurrence of gastric cancer has been attributed mainly to cigarette smoking [12]. The overall 5-year survival for gastric cancer is only 5–15% because many patients present at a late stage [2]. Therefore it is important to continually explore new improved therapeutic agents for this cancer.

The most commonly administered single agent, 5-fluorouracil (5-FU), has been reported to have a 21% overall response rate. Single-agent etoposide has resulted in response rates ranging from 10% to 20% [18]. Chemotherapy regimens utilized for gastric cancer often include the following combinations: 5-FU/high-dose methotrexate/doxorubicin, etoposide/doxorubicin/cisplatin, etoposide/5-FU/leucovorin, epirubicin/cisplatin/5-FU. Response rates with these regimens range from 25% to 40%, with a median survival of 6–8 months in patients with metastatic disease [11]. In Japan, 5-FU- and cisplatin-based combination chemotherapy is preferred over regimens which incorporate an anthracycline [17]. In Taiwan, a regimen based on weekly 24-h 5-FU infusion is usually given up-front with responses ranging...
from 40% to 80% and median survival of 8–11 months [4, 5, 13]. Administration of 5-FU by infusion is preferred since thymidylate synthase inhibition by 5-FU is significantly greater in patients given 5-FU by continuous infusion than by bolus injection [19].

With infusion 5-FU as a backbone, the challenge lies in the selection of efficacious agents to be given in combination. Cisplatin [16], the taxanes [11], and camptothecins [3, 11] have all shown promise. New developments in topoisomerase inhibitors include oral etoposide [1], but a more efficacious epipodophyllotoxin would be better. GL331 is a new etoposide analogue whose principle mechanism of action is through inhibition of topoisomerase IIα (T2α) [8]. Overexpression of T2α is usually predictive of etoposide responsiveness [20]. GL331 has the added advantage over etoposide of having a higher affinity for transport into the cancer cell, and thus the potential to circumvent drug resistance attributed to mdr1 gene overexpression [9, 10]. A phase II and pharmacokinetic (PK) study was initiated to ascertain the efficacy and toxicity of GL331 in previously treated Chinese patients, with concomitant determination of the initial tumor T2α content.

Patients and methods

This study was approved by the Taipei Veterans’ General Hospital Ethics Committee and the Department of Health of the Republic of China.

Patients

All patients provided informed consent to the protocol treatment. Eligibility criteria included: proof of gastric cancer pathology; at least one bidimensionally measurable lesion; progression after first-line treatment; Eastern Cooperative Oncology Group (ECOG) perfor-

ation status £ 1.5 mg/dl) and renal function (creatinine £ 2 mg/dl); adequate absolute neutrophil count (ANC) (£1500/mm3) and platelet count (£100,000/mm3). Assessment of response was according to ECOG criteria, and evaluation of toxicity was according to the common toxicity criteria [14].

Follow-up studies

Full blood counts were obtained weekly during the first course to monitor nadir white cell count and ANC, and blood chemistry study was done prior to each course of GL331. Tumor marker studies, coagulation profiles, and imaging studies for measurement of tumor status were performed every 3–4 weeks during the first two courses in order to detect any rapidly regressive or progressive disease, and then after every two courses.

Drug administration

GL331 has a molecular formula of C27H24N2O9. It is formulated in a vehicle consisting of 8% Tween-80 dissolved in a mixture of 62% polyethylene glycol 300 and 30% absolute ethanol [8, 10]. The maximum tolerated dose determined in the phase I trial was 300 mg/m2 as a 3-h infusion for five consecutive days every 3–4 weeks [8]. Our starting dose was therefore set at 200 mg/m2 given in 2000 ml normal saline (using non-PVC containers and tubing) in the same schedule, and if tolerable, with rapid escalation in 20% fractions every subsequent cycle. Premedication was not advised unless the patient vomited, and subsequent prescription of oral metoclopramide was considered sufficient. A 20% dose reduction would be instituted for a nadir ANC £ 500/mm3 or platelet count £ 50,000/mm3, and a 20% dose escalation would be instituted if the nadir ANC was £1000/mm3 and platelet count was £100,000/mm3. Treatment was to be stopped if progressive disease occurred, but continued for stable or responsive disease. Overall survival was counted from the day of initiation of GL331, and progression-free survival was counted from the day of treatment until disease progression. Survival was analyzed according to the Kaplan-Meier method.

Pharmacokinetics

A PK study was performed during the first course of treatment. High-performance liquid chromatography (HPLC) was performed using a Hewlett Packard 1100 system with elution peaks at 394 nm. Blood samples were drawn via an indwelling venous catheter, and 3-ml aliquots were spun down at 800 rpm for 4 min and the plasma stored at –80°C until analysis. The zero time-point was completion of the 3-h GL331 infusion on the 5th day of treatment. Blood samples for the PK study were taken at –48, –24, 0, 1, 2, 3, 4, 6, 8, 12, 48, 60, 84 and 96 h, a total of 16 sampling points. Systemic clearance, volume of distribution, and parent drug elimination half life were evaluated using WinNonlin software based on a two-compartment model.

Immunohistochemistry

Immunohistochemical evaluation of 11 available specimens was carried out using a T2α antibody (gift from Dr J.L. Huang, Academia Sinica, Taiwan). Briefly, 4-μm thick paraffin sections were cut, fixed, deparaffinized and stained with the primary T2α antibody. A LSAB-2 kit (DAKO, Carpinteria, California) was used for detection. Overexpression was considered to be present if the nucleus of the cancer cells showed red staining.

Statistics

Statistical analysis was based on a projected response rate of 20%. Accepting a 4% rejection error (α), a minimum of 14 patients would be needed for the study. Thus, for a true 20% response rate, the chance of observing 14 consecutive failures would be less than 5% [7].

Results

A total of 15 previously treated gastric cancer patients were enrolled in this study (Table 1). All had adenocarcinoma of the stomach. Pathology was diagnosed by endoscopic biopsy in 2 patients, and 13 others underwent laparotomy. One patient had inoperable disease and all the others received partial or total gastric resection.

The first patient developed renal insufficiency with decreased urine output on the 3rd day of treatment for reasons unrelated to GL331. GL331 was stopped in this patient but he was still evaluated for response and toxicity on an intention to treat basis. A total of 35 courses were delivered, with one to six courses per patient. Ten patients completed at least two courses, four patients