RESEARCH COMMUNICATION

Clinical Observations on Safety of Fixed Dose Rate Gemcitabine Chemotherapy by Intravenous Infusion

Cheng-Yun Yao[1], Xin-En Huang[1*], Jin-Hai Tang[2*], Hong-Xia Xu[1]

Abstract

Purpose: To observe the safety of fixed dose rate gemcitabine by intravenous infusion (iv-FDR) for cancers. Methods: From January 1, 2007 to December 31, 2009, four patients who were pathologically diagnosed with advanced pancreatic or breast cancer were recruited into this study. They were treated by gemcitabine 10mg/m2/min iv-FDR on days 1 and 8, and combined with other chemotherapeutics, repeated every four weeks. Toxicity was determined in line with the National Cancer Institute-Common Toxicity Criteria (NCI-CTC). Results: The main toxicity was reversible myelosuppression; other side effects included gastrointestinal toxicity and liver impairment. Cardiac or renal toxicity was not detected. Conclusion: The toxicity of iv-FDR gemcitabine combination chemotherapy was well tolerated, so that iv-FDR gemcitabine deserves to be further studied as a treatment option.

Keywords: Gemcitabine - fixed dose rate - chemotherapy - toxicity

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Introduction

Gemcitabine (2',2'- difluorodeoxycytidine) is nucleoside analog antimetabolite, initially phosphorylated by deoxycytidine kinase to gemcitabine monophosphate, and further yield gemcitabine diphosphate and gemcitabine triphosphate (dFdCTP)(Heinemann et al., 1988), which is the main active metabolite of gemcitabine that yield efficacy. Gemcitabine diphosphate inhibits ribonucleotide reductase (Heinemann et al., 1990), decreasing the cellular pool of deoxycytidine triphosphate that competes with dFdCTP for incorporation into DNA, and inhibits replication with subsequent induction of apoptosis (Huang et al., 1991; Huang et al., 1995). The potent cytotoxic effect of gemcitabine has been well demonstrated in the treatment of pancreatic and lung cancer (Noble et al., 1997). At present, clinical studies on gemcitabine in the treatment of other cancers are very active, from renal and hepatocellular carcinoma to soft tissue sarcoma being continuously reported (Guan et al., 2003; Massacesi et al., 2005; Attia et al., 2009). In almost all clinical researches on gemcitabine, 30-minute intravenous infusion is considered a standard way of administration (Martin et al., 1996).

However, phosphorylation of gemcitabine to the monophosphate by deoxycytidine kinase is the rate-limiting step in the accumulation of the active diphosphate and triphosphate metabolites (Grunewald et al., 1990). Grunewald and Abbruzzese demonstrated in vivo in early phase I studies that the ability of mononuclear cells to accumulate dFdCTP during therapy was saturable, and that the optimal plasma concentration of gemcitabine that maximized the rate of formation of dFdCTP was approximately 20 μmol/L(Grunewald et al., 1990; Abbruzzese et al., 1991). In these studies, this target gemcitabine concentration in plasma was achieved, and the rate of dFdCTP accumulation by mononuclear cells and leukemia cells was optimized using dose rates approximating 10 mg/m^2/min, which may yield a better efficacy.

Therefore, we hypothesized that Chinese patients will benefit from gemcitabine that is intravenously infused at a fixed dose rate (FDR) of 10mg/m^2/min.

Materials and Methods

Patient selection

Eligible criteria included: 1.patients who were treated with FDR gemcitabine should have pathologically diagnosed with advanced or metastatic cancer and with at least a measurable disease, and hospitalized at the Department of Chemotherapy of Jiangsu Cancer Hospital and Research Institute from 2007; 2.with karnofsky performance status ≥60 and life expectancy ≥3 months; 3.with adequate bone marrow reserve (white blood cell count ≥3.5 x 10^9/L, platelets ≥100 x 10^9/L, hematocrit ≥30%, and hemoglobin ≥10 g/L); 4.with adequate organ function, levels of creatinine, liver enzymes and alanine aminotransferase less than two times the upper limits of normal; 5.signed treatment consent before chemotherapy.

Study design

Patients were treated with gemcitabine at a rate of 10

*[1]Department of Chemotherapy, [2]Department of Surgery, Jiangsu Cancer Hospital and Research Institute, Nanjing, China * For Correspondence: zgzlwk@139.com, huangxinen06@yahoo.com.cn*

Table 1. Patient Characteristic

Characteristic	Patient1	Patient2	Patient3	Patient4
Age(year)	51	48	53	74
Gender	male	female	female	female
Histology of cancer	pancreatic	breast	breast	breast
Stage	IV	IV	IV	IV
Karnofsky performance status	60	80	70	70
Chemotherapy regimens	Gemcitabine	Gemcitabine +Cisplatin	Gemcitabine +Cisplatin	Gemcitabine+Docetaxel
Chemotherapy cycle	2	6	1	2
Response	PD	SD	SD	SD
Toxicity*				
Hematological*	1	3	1	2
Nonhematological*	1	1	1	0

*NCI CTC toxicity grade; PD: progressive disease; SD: stable disease

mg/m^2/min intravenous administration, and combinated with other cytotoxic agents. Gemcitabine 1000mg/m^2 was delivered weekly on day 1 and day 8 and repeated every four weeks. Conventional antiemetic drugs were administrated before and during chemotherapy.

Evaluation Criteria

Response was evaluated according to Response Evaluation Criteria in Solid Tumors criteria (Therasse et al., 2000). Toxicity was evaluated according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (Kaba et al., 2004). The toxicity would be evaluated after the completion of a cycle.

Results

Four patients were recruited into study from January 1,2007 to December 31,2009. Diagnose of one patient was pancreatic cancer, the others were breast cancer. The patient characteristics were displayed in Table 1. Of the four patients assessable for chemotherapy response, three patients had stable disease (SD), one patient had progressive disease (PD). All patients were evaluated for toxicity. One patient had grade 3 neutropenia (25%), one anemia (25%), the other had grade 1 hematological toxicity. Nonhematological toxicity including grade 1 hepatic function impairment (75%), toxicities for each patient are summarized in Table 1, other nonhematological toxicity (including gastrointestinal reactions, hypodynamia, anorexia and constipation) were observated in patients, but the occurrence probability was rare without grade 3 or 4 toxicity. No obvious heart and kidney toxicity were observated.

Discussion

Due to pharmacological features of gemcitabine, a longer infusion time would provide increased intracellular concentration of tumor tissues, thus enhancing the efficacy of agents (Grunewald et al., 1990; Abbruzzese et al., 1991). In a randomized phase II trial, Tempero et al. compared gemcitabine FDR infusion with the standard 30 minute infusion in a group of pancreatic cancer patients (Tempero et al., 2003), the median survival time(MST) (8.0 months vs 5.0, P=0.013), 1-year survival rate(28.8% vs 9%, P=0.014) and 2-year survival rate (18.3% vs 2.2%, P=0.007) of FDR infusion are superior to those of standard method. Phase III, randomized trial of the Eastern Cooperative Oncology Group in pancreatic cancer patients showed a better MST and 1-year survival were 6.2 months and 21% for gemcitabine FDR (HR, 0.83; stratified log-rank, P=0.04) than standard gemcitabine 30 minute infusion (4.9 months and 16%)(Poplin et al., 2009). The FDR infusion of gemcitabine allows maximal intracellular accumulation of the active triphosphate form of the drug, and thus may result in better antitumor activity.

The study of two-weekly gemcitabine FDR and oxaliplatin combination chemotherapy for advanced non small cell lung cancer (NSCLC) by Früh et al. showed the MST 10.4 months, 1-year survival rate 42% and a surprising response rate of 81% (Früh et al., 2008). Another phase II clinical investigated gemcitabine FDR infusion combinated with Cisplatin and UFT in the first line treatment of advanced NSCLC. Three percent patients achieved complete response, 46% partial response and 27% SD, the MST was 14.7 months, 1-year survival rate was 54% (Poplin et al., 2009). Thus, FDR infusion of gemcitabine was considered effective in the first line treatment of advanced NSCLC patient.

In the previous study of Tempero et al, grade 3/4 hematologic toxicities of FDR infusion were well documented, patients seem to experience more grade 3/4 thrombocytopenia (37.2% v 10.2%), neutropenia (48.8% v 26.5%), and grade 4 anemia (9.3% v 2%) than 30 minute infusion (Tempero et al., 2003). Grade 3 hematologic toxicity was 37%, grade 3 anaemia and thrombocytopenia were 19% and 5% respectively in the study of Shin et al (Shin et al., 2008). This is consistent with study reported by Poplin et al, in which grade 3/4 neutropenia and thrombocytopenia were more common with gemcitabine FDR (Poplin et al., 2009).

In our present study, one patient in our study had grade 3 hematologic toxicity, we found this patient had been treated with 6 cycles chemotherapy, the response was SD, but iphosphamide was added to the sixth cycle which may aggravate the toxicity. Other patients had no grade 3 or 4 toxicities.

Pharmacokinetics study suggests gemcitabine 1000 mg/m^2 can be administered as an FDR infusion in patients with altered hepatic function without causing additional toxicity compared with patients with normal hepatic function (Felici et al., 2009). In our study, the hepatic

function of one patient who had grade 1 impairment before chemotherapy was not worsen during and after treatment, which is consistent with that study reported.

The reason of higher hematologic toxicity of gemcitabine FDR infusion is unclear, the findings (Gandhi et al., 1990; Grunewald et al., 1990) indicate that the dose rate of 10mg/m^2/min should be sufficient to maximize dFdCTP accumulation by cells in plasma, also most likely in the bone marrow, because of the largely sinusoidal nature of this tissue. But futher studies have been not discussed in present.

In summary, it was safe that FDR infusion of gemcitabine was treated with advanced cancer patients of our population, nonhematologic toxicities response were mild, but hemotologic toxicities were significant which need especially pay attention to. Suitable patients should be recommended to administer in clinical future studies. The efficacy of FDR gemcitabine is superior to standard intravenous infusion or not still need to be confirmed by controlled trials.

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