

ORIGINAL ARTICLE

## Administration of gemcitabine and cisplatin in cancer patients with renal failure under hemodialysis

Ping-Ying Chang, Ming-Shen Dai, Ching-Liang Ho, Nai-Shun Yao

Division of Hematology/Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

### Summary

**Purpose:** There is no optimal dosing schedule of gemcitabine (GEM) and cisplatin (CDDP) combination for cancer patients with renal failure (RF) on hemodialysis (HD). The purpose of this study was to share our experience of using GEM and CDDP in such patients.

**Methods:** The starting dose of GEM was defined based on single-agent treatment of two cancer patients with RF. Between November 2006 and June 2009, 4 RF cancer patients on HD received a GEM and CDDP combination chemother-

apy (CDDP 30mg/m<sup>2</sup> on days 1, 8, 15 and GEM 600mg/m<sup>2</sup> on day 15; repeated every 28 days). The HD was conducted within 24 hours after the completion of GEM and/or CDDP administration.

**Results:** Reduced-dose GEM and CDDP combination showed efficacy and good tolerability for cancer patients with RF under HD.

**Key words:** cisplatin, gemcitabine, hemodialysis, renal failure

### Introduction

GEM (2',2'-difluorodeoxycytidine) and CDDP have been used as a combination to treat various malignancies including non-small cell lung cancer (NSCLC) and urothelial cell carcinoma (UCC) [1-4]. Both of these drugs are excreted mainly via the kidney and therefore adequate renal function is necessary for standard dosing. However, renal impairment is not uncommon among this group of patients. Many co-morbid medical conditions, cancer progression, and prior anti-neoplastic treatments including nephrectomy may be contributing factors. In addition, higher incidence of kidney and urinary tract cancer has been reported in patients on long term HD [5]. There is a huge unmet medical need in terms of chemotherapy dosing guidelines in this group of patients. There are published data regarding the dosing and usage of these two agents in a general sense but the optimal dose and schedule of GEM and CDDP for RF patients on HD have never been defined. The aim of this report was to share our experience of

using GEM and CDDP in the treatment of such patients.

### Methods

Venook et al. conducted a phase I and pharmacokinetic (PK) study of GEM (CALGB 9565 trial) in patients with renal dysfunction (creatinine level 1.6 to 5.0 mg/dL). Dose-limiting toxicities were noted in 4 of the 15 patients even at reduced dose (650 and 800/m<sup>2</sup>) [6]. Based on the results of this study, we started treatment with reduced dose of GEM in 2 cancer patients with RF in August 2006 in an attempt to define the optimal starting dose of GEM in such patients. Based on the experience acquired from these 2 cases we proceeded to treat another 4 patients. Treatment efficacy was measured by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and toxicity was assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.

### Results

Patient and disease characteristics are summarized in Table 1.

**Table 1.** Patient and disease characteristics (before treatment)

Patient no.	Sex/Age (years)	ECOG PS	Co-morbidities	Diagnosis	TNM stage
1	F/62	1	No	UCC of both ureters	T3NxM0
2	F/75	2	DM, HTN	Locally advanced pancreatic cancer	T4NxM0
3	M/53	1	HTN	UCC of the bladder	T3N1M0
4	M/32	1	No	UCC of both ureters, bladder	T3N0M1
5	F/52	1	DM, HTN	NSCLC	T2NxM1
6	M/70	1	Liver cirrhosis, HTN, CAD	NSCLC	T4N3M1

DM: diabetes mellitus, HTN: hypertension, CAD: coronary artery disease, HD: hemodialysis, UCC: urothelial cell carcinoma, NSCLC: non-small cell lung cancer

**Table 2.** Clinical treatment outcomes

Patient no.	Response	Cycles	TTP (months)	Toxicities
1	CR	1	-	grade 4 neutropenia, grade 3 hepatotoxicity
2	SD	6	5	grade 4 neutropenia, grade 3 thrombocytopenia
3	PD	4	3	grade 1 neutropenia
4	PR	40*	-	grade 2 neutropenia, grade 3 thrombocytopenia
5	PR	4	4	grade 1 neutropenia, grade 3 thrombocytopenia
6	PR	3	3	grade 1 thrombocytopenia grade 2 hepatotoxicity

\*Still on treatment

TTP: time to progression, CR: complete response, PR: partial response, SD stable disease, PD: progressive disease

### Case 1

A 62-year-old woman with RF was diagnosed with high-grade invasive UCC of both ureters and the left renal pelvis (cT3NxM0) in July 2006. Her baseline BUN, creatinine and creatinine clearance were 75 mg/dL, 8.1 mg/dL, and 4.16 ml/min, respectively. Considering her impaired renal function at baseline, the patient received neoadjuvant chemotherapy with single-agent GEM with the first dose at 700 mg/m<sup>2</sup> in August 2006. General weakness was noted and the dose was reduced to 400 mg/m<sup>2</sup> in the second week. She experienced grade 4 neutropenia and grade 3 hepatotoxicity after these two doses of treatment. The patient then underwent bilateral nephrectomy and radical cystectomy in October 2006 which revealed pathologic CR. Regular HD was started after the operation and the patient has remained disease-free up until now.

### Case 2

A 75-year-old woman with RF on HD was diagnosed with locally advanced pancreatic cancer (cT4NxM0) in July 2006. Her baseline pre-HD

BUN, serum creatinine and creatinine clearance were 40 mg/dL, 8.2 mg/dL, and 0 ml/min, respectively. She received the first dose of GEM 400 mg/m<sup>2</sup> in August 2006 but she experienced grade 4 neutropenia and grade 2 thrombocytopenia. The dose was then reduced to 300 mg/m<sup>2</sup> weekly (three weeks on and one week off). She achieved SD after 3 cycles of treatment and GEM was continuously administered for 6 months until deterioration of her condition. Grade 4 neutropenia and grade 3 thrombocytopenia occurred during treatment. Neutropenia could be managed by granulocyte colony stimulating factor and thrombocytopenia was self-limited without need for platelet transfusions.

### Four subsequent cases

Based on a review of the literature and our preliminary experience with the above 2 cases, we treated 4 cancer patients (2 UCCs and 2 NSCLCs) with RF on HD with GEM plus CDDP. In a 28-day treatment cycle, we planned to deliver GEM only on day 15 with a dose of 600 mg/m<sup>2</sup> because of the significant toxicities observed in the weekly schedules with our first 2 cases. GEM dosage

was allowed to be escalated or reduced by 30% depending on the grade 3 or 4 toxicities that occurred in the prior cycle. As for CDDP, we planned to deliver it on a weekly schedule at a dose of 30 mg/m<sup>2</sup> on days 1, 8 and 15 according to the report by Zahara et al. [17]. Standard HD was performed within 24 hours after the completion of GEM and/or CDDP administration.

All 4 patients tolerated the treatment quite well. The main toxicities were hematological. Three patients achieved PR and one failed to respond and experienced PD. All patients received at least 3 courses of treatment and one is still in a stabilized PR 6 years after the diagnosis. As for the GEM dose, dose reduction was necessary in one patient while in the 3 others the dosage increased in the subsequent treatment courses. The treatment details and patient outcomes are summarized in Table 2.

## Discussion

Our study showed that reduced-dose combination of GEM and CDDP can be administered safely and effectively in RF patients under HD who have NSCLC and UCC.

GEM is phosphorylated to diphosphate (dFdCDP) and triphosphate (dFdCTP) forms in the cells. Incorporation of dFdCTP into DNA can lead to termination of the DNA synthesis and cell death. GEM is rapidly metabolized in the liver, kidneys and other tissues to a metabolite 2',2' difluorodeoxyuridine (dFdU) after intravenous administration. Elimination of dFdU depends on renal function [1].

Several pharmacokinetic studies of GEM have been performed in the patients with impaired renal function but the results are inconsistent [6-9]. Venook et al. reported that the pharmacokinetics profiles of GEM have no obvious differences between patients with impaired renal function and those with normal renal function. However, increased toxicities are observed in patients with elevated serum creatinine level even with reduced dose [6]. By using the dose schedule of GEM 1000 mg/m<sup>2</sup> on days 1 and 10 followed by standard HD in RF patients, Kiani et al. reported that the pharmacokinetics profiles of GEM are the same as those with normal renal function. However, markedly decreased clearance of dFdU was found and the authors confirmed that dFdU can only be partially eliminated by HD [7]. A variety of options for GEM dosing has been proposed

[7-10]. One report suggested that GEM 800-1000 mg/m<sup>2</sup> can be safely administered in RF patients on HD, especially soon after commencing HD, as long as HD is initiated within 24 hours after GEM administration [11].

Though the results of the aforementioned reports are not consistent, we observed significant toxicities with GEM in one patient, even with dose reduction in the current study. GEM and dFdCTP are unlikely to be the direct cause of toxicities in RF patients on HD because both of them are easily removed by HD [6,7]. Prolongation of terminal half-life and increase in the AUC of plasma dFdU in RF patients have been consistently reported [7,8,11]. dFdU was previously believed to be an inactive metabolite. Emerging evidence shows that dFdU may in fact exert cytotoxic activity at high serum levels. Intracellular phosphorylation to dFdU triphosphate has been considered to be the likely reason [8,12]. In our own experience, dose reduction of GEM did not seem to compromise the treatment efficacy (1 CR, 3 PR and 1 SD out of 6 patients). Therefore, it is reasonable to surmise that dFdU is an active metabolite that has cytotoxic effects. Since dFdU can only be partially removed by HD, reduced doses of GEM would be appropriate for these patients.

The dosing schedule of CDDP in patients with RF on regular HD is also controversial [13,14]. The timing of HD after the delivery of CDDP varied in different reports [15,16]. Zahara et al. found that concurrent chemoradiotherapy with weekly CDDP 25mg/m<sup>2</sup> was safe and HD could be delayed more than 3 hours after infusion [17]. We treated our 4 patients with weekly CDDP and reduced GEM dosage and HD was performed within 24 hours after GEM and/or CDDP administration.

With the above approach, we observed only mild to moderate toxicities, which were primarily hematological in nature. We also saw good treatment responses. Three PRs were observed among 4 patients with overall response rate of up to 75%. Moreover, one PR patient remains stabilized PR up until now.

In conclusion, despite the small number of patients in this study, we observed a consistent trend of treatment response and acceptable toxicity profiles with reduced GEM dose plus weekly CDDP in cancer patients with RF on regular HD. Also, our data indirectly suggests that dFdU is an active metabolite with cytotoxic activity.

This dose and schedule of GEM and CDDP combination could be delivered safely and ef-

fectively in RF patients on regular HD. Further well-designed prospective pharmacokinetic studies in such patients are warranted to confirm our observations. Until then, we believe that this report will serve as another useful reference for clinicians treating this challenging group of patients with little guidance from the current published literature.

## Acknowledgement

The authors extend their thanks to Dr. Vivek R. Sharma, research scientist and medical director, adult hemophilia program, division of medical oncology/hematology, University of Louisville, School of Medicine for his critical review and comments on this manuscript.

## References

1. Storniolo AM, Allerheiligen SR, Pearce HL. Preclinical, pharmacologic, and phase I studies of gemcitabine. *Semin Oncol* 1997;24(2 Suppl 7):S2-S7.
2. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999;17:409-422.
3. Schiller JH, Harrington D, Belani CP et al. Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92-98.
4. von der Maase H, Sengelov L, Roberts JT et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23:4602-4608.
5. Stewart JH, Buccianti G, Agodoa L et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. *J Am Soc Nephrol* 2003;14:197-207.
6. Venook AP, Egorin MJ, Rosner GL et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. *J Clin Oncol* 2000;18:2780-2787.
7. Kiani A, Köhne CH, Franz T et al. Pharmacokinetics of gemcitabine in a patient with end-stage renal disease: effective clearance of its main metabolite by standard hemodialysis treatment. *Cancer Chemother Pharmacol* 2003;51:266-270.
8. Koolen SL, Huitema AD, Jansen RS et al. Pharmacokinetics of gemcitabine and metabolites in a patient with double-sided nephrectomy: a case report and review of the literature. *Oncologist* 2009;14:944-948.
9. Pini TM, Rothenberg ML, Nicol S, Kaplan M, Egorin MJ. Pharmacokinetics of gemcitabine in a patient with renal failure on hemodialysis. *Proc Am Soc Clin Oncol* 22:2003 (abstr 630).
10. Masumori N, Kunishima Y, Hirobe M et al. Measurement of plasma concentration of gemcitabine and its metabolite dFdU in hemodialysis patients with advanced urothelial cancer. *Jpn J Clin Oncol* 2008;38:182-185.
11. Matsuda M. Gemcitabine for patients with chronic renal failure on hemodialysis. 2007 ASCO Annual Meeting Proceedings Part I. *J Clin Oncol* 2007;25 (18 S):15189 (abstr).
12. Veltkamp SA, Pluim D, van Eijndhoven MA et al. New insights into the pharmacology and cytotoxicity of gemcitabine and 2',2'-difluorodeoxyuridine. *Mol Cancer Ther* 2008;7:2415-2425.
13. Tomita M, Aoki Y, Tanaka K. Effect of haemodialysis on the pharmacokinetics of antineoplastic drugs. *Clin Pharmacokinet* 2004;43:515-527.
14. Watanabe R, Takiguchi Y, Moriya T et al. Feasibility of combination chemotherapy with cisplatin and etoposide for haemodialysis patients with lung cancer. *Br J Cancer* 2003;88:25-30.
15. Gorodetsky R, Vexler A, Bar-Khaim Y, Biran H. Plasma platinum elimination in a hemodialysis patient treated with cisplatin. *Ther Drug Monit* 1995;17:203-206.
16. Lagrange JL, Cassuto-Viguiet E, Barbé V et al. Cytotoxic effects of long-term circulating ultrafiltrable platinum species and limited efficacy of haemodialysis in clearing them. *Eur J Cancer* 1994;30A:2057-2060.
17. Zahra MA, Taylor A, Mould G, Coles C, Crawford R, Tan LT. Concurrent weekly cisplatin chemotherapy and radiotherapy in a haemodialysis patient with locally advanced cervix cancer. *Clin Oncol (R Coll Radiol)* 2008;20:6-11.