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REVIEW

Prolonged low-dose infusion for gemcitabine: a systematic review

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Background: The present standard dose of gemcitabine (Gem), a pyrimidine antimetabolite, is 1,000–1,250 mg/m^2, and the infusion time is 30 min. However, pharmacological studies have demonstrated that Gem with prolonged infusion could attain a better accumulation rate of Gem triphosphate (active metabolites of Gem), indicating that Gem with prolonged infusion is superior to 30-min infusion. Thus, this systematic review aims to provide some references for Gem administered as a prolonged infusion.

Methods: We searched electronic databases, including PubMed, EMBASE, Cochrane Library, and CNKI, for trials. Keywords were "Gem," "prolonged infusion," and "low-dose." In addition, we used the Cochrane Handbook V5.1.0 and methodological index for non-randomized studies to evaluate the quality of randomized controlled trials (RCTs) and non-RCTs, respectively. Furthermore, Cochrane Collaboration guidelines and the PRISMA statement were adopted.

Results: We systematically reviewed 19 studies (5 RCTs and 14 non-RCTs). All studies assessed the efficacy and safety of Gem administered as a prolonged low-dose infusion (P-LDI) and reported that Gem administered as P-LDI was effective and well tolerated.

Conclusion: Gem administered as P-LDI is effective, safe, and economical, especially suited for patients with poor performance status or without good economic condition.

Keywords: gemcitabine, low dose, prolonged infusion, pharmacokinetics

Introduction

Gemcitabine (Gem) is related to specific inhibition of DNA synthesis and commonly used as therapy for various solid tumors, including non-small cell lung cancer (NSCLC), nasopharyngeal carcinoma, and pancreatic cancer.[1] Reportedly, Gem is a pro-drug that needs to be phosphorylated to Gem triphosphate by deoxycytidine kinase (DK).[2] DK is a rate-limiting enzyme during the activation of Gem and saturated at Gem concentration >20 μmol/L.[3] Thus, a linear correlation between the intracellular accumulation of Gem triphosphate and Gem concentration can only be expected at the plasma concentration below 20 μmol/L.[2] In addition, it has been established that the plasma concentration of Gem following 30-min infusion often exceeds the saturation concentration of DK. Hence, the short-term infusion leaves a majority of the drug unmetabolized and might not be the best method for Gem administration. Conversely, by prolonging the infusion time, the accumulation rate of Gem triphosphate could be elevated and, possibly, achieve better clinical efficiency.[4]

For the standard 30-min infusion, the maximum tolerated dose (MTD) is ≥1500 mg/m^2.[5] With the infusion time prolonging for 3,4, 6, or 24 h, MTD significantly falls to

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450, 200, 300, and 180 mg/m^2, respectively;[4–8] this phenomenon can be explained by saturation of DK.

In clinical practice, Gem administered as a 30-min infusion of 1,000–1,250 mg/m^2 is the standard regimen. However, several trials[9–12] have demonstrated that another type of administration [prolonged low-dose infusion (P-LDI)] exhibits a comparable activity and toxicity compared with a 30-min infusion of the standard dose (30-min SDI). Previously, we suggested that P-LDI was superior in terms of the overall response rate, experienced less grade 3/4 thrombocytopenia and leukopenia compared with 30-min SDI, and could be a viable treatment option for advanced NSCLC.[9] However, whether the same is also applicable to other cancer types remains unclear. Hence, this systematic review of the current literature aims to provide some references for Gem administered as a prolonged infusion and supports the need for further investigation regarding both clinical efficiency and safety.

Methods

Search strategy

We searched electronic databases, including PubMed, EMBASE, Cochrane Library, and CNKI. The search was limited to studies written in English and Chinese, and articles published from the earliest entries of any databases until February 2019. Keywords were "gemcitabine," "GEM," "prolonged low-dose infusion," "prolonged infusion," "long infusion," "low dose," and "standard dose". Furthermore, manual searching of references from the included studies and the websites of clinical trials were examined for additional relevant articles.

Eligibility criteria

In this review, the inclusion criteria were as follows: studies were clinical trials written in English and Chinese, and Gem administered as P-LDI. However, we excluded case reports, conference abstracts, literature reviews, meta-analyses, and animal model studies.

Data extraction and data items

Data were extracted from eligible studies and reviewed independently by two investigators. The items extracted from each study included first author, publication date, journal, study design, tumor types, chemotherapy regimens, number of patients, age, sex, overall survival (OS), progression-free survival (PFS), and 1-year survival rate (1-YSR). In addition, we contacted the authors of the primary studies for missing data; if we were unable to contact the authors, we excluded the study.

Reviewing quality based on the checklist

We used the Cochrane Handbook V5.1.0 and methodological index for non-randomized studies (MINORS) to assess the quality of randomized controlled trials (RCTs) and non-RCTs, respectively.

Results

Eligible studies

Using the search strategy, we identified 1242 studies. Then, we examined the title, abstract, and excluded 1214 studies. Finally, we included 19 studies after a full-text review (Figure 1). Table 1 summarizes the characteristics of the selected studies.

Quality and publication bias of included trials

In this systematic review, we selected 5 RCTs and 14 non-RCTs. We used Cochrane Handbook V5.1.0 and MINORS for RCTs and non-RCTs, respectively, to assess the risk of bias of the selected studies. Of five RCTs, two trials detailed the sequence generation and blinding, but none detailed the allocation concealment, selective reporting, or other sources of bias (Table 2). Of 14 non-RCTs, MINORS scores ranged 6–11, demonstrating the existence of a significant amount of methodological heterogeneity among studies (Table 1).

Clinical application of gem in P-LDI

Based on possible advantages of Gem administered as P-LDI, several phase I and II clinical trials have reported significant antitumor activity of Gem administered as P-LDI. Table 3 presents the spectrum of diseases, including cancer of the lung, pleural, breast, pancreas, gallbladder, bladder, sarcomas, and soft tissue.

NSCLC

Beniwal[10] investigated the efficacy and safety of the combination of Gem administered as P-LDI compared with 30-min SDI and carboplatin in patients with NSCLC. Overall, 60 patients with stage III_B/IV NSCLC were randomly assigned to P-LDI and 30-min SDI. The ORR was 40% and 36.6%, SDR was 33.3% and 36.3%, PDR was 26.6% and 26.6%, PFS was 5.5 and 5.4 months, OS was 9.7 and 10.7 months, and 1-YSR was 33.7% and 36.6% in 30-min

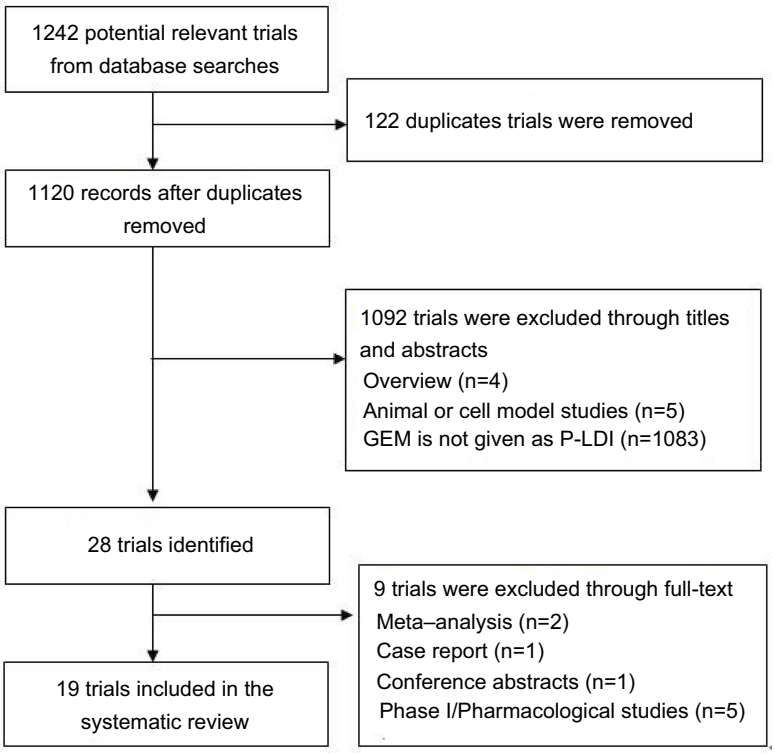

Figure 1 Flowchart of included and excluded trials.

SDI and P-LDI, respectively. Notably, grade 3/4 toxicities were rare. Owing to good efficacy, low toxicity, and lower drug costs, Gem administered as P-LDI is an attractive option for the elderly or those without good economic condition.

Vrankar[11] presented a phase II randomized trial of induction chemotherapy comparing Gem in two different schedules with cisplatin followed by concurrent radiochemotherapy in locally advanced NSCLC. In their study, toxicities were comparable and mild in both arms. The PFS was 15.7 and 18.9 months, OS was 24.8 and 28.6 months, 1-YSR was 73.1% and 81.5%, and 3-YSR was 30.8% and 44.4% in 30-min SDI and P-LDI, respectively. Although we observed a trend toward better efficacy of the treatment with prolonged infusion, the difference between the two arms was not statistically significant.

In the trial conducted by Zwitter,[12] the PFS was 5.5 and 6 months, OS was 10.1 and 10 months, and 1-YSR was 46.6% and 41.1% for 30-min SDI and P-LDI, respectively. Moreover, grade ≥3 toxicities were rare. The study suggested that P-LDI could be preferred for incurable cancer among economically deprivileged patients. In addition, other trials demonstrated the efficacy and safety of Gem administered as P-LDI,[13–16] suggesting that P-LDI was effective and well tolerated for NSCLC. Furthermore, a meta-analysis of 6 RCTs[17] reported that P-LDI was superior in terms of ORR, experienced less grade 3/4 thrombocytopenia and leukopenia compared with 30-min SDI, and could be a viable treatment option for advanced NSCLC.

Malignant pleural mesothelioma

After favorable experience with Gem administered as P-LDI for advanced NSCLC, Kovac[18] conducted a phase II trial on patients with malignant pleural mesothelioma (MPM); 78 patients were treated with Gem administered as P-LDI plus cisplatin for four cycles. Grades 3/4 toxicities were anemia in 2 patients, neutropenia in 18 patients, and nausea/vomiting in 1 patient. The PFS, OS, 1-YSR, 2-YSR, and 3-YSR were 8 months, 17 months, 67.3%, 32.7%, and 19.8%, respectively. Hence, Gem administered as P-LDI with cisplatin could be considered for the primary treatment of MPM, especially in economically deprived populations.

Arrieta conducted another phase II trial of Gem administered as P-LDI plus cisplatin in patients with advanced MPM.[19] The PFS and OS were 6.9 and 20.7 months. In

Table 1 Characteristics of eligible trials

Trial	Study design	Patients	Male/ female	Age	Tumor type	Chemotherapy regimens	Endpoints assessed	MINORS Score
Beniwal SK, 2012[10]	RCT	30	26/4	53.3 (35~65)	NSCLC	GEM (1,000 mg/m^2 in 30 min d1, d8)+ CBP(AUC 5 d1)	ORR SDR PDR PFS OS 1-YSR	N/A
		30	28/2	54.5 (40~70)		GEM (350 mg/m^2 in 6 h d1, d8) +CBP (AUC 5 d1)		
Vrankar M 2014[11]	RCT	52	39/13	58 (42~72)	NSCLC	GEM (1250 mg/m^2 in 30 min d1, d8)+ DDP (75 mg/m^2 d2)	PFS OS 1-YSR ORR	N/A
		54	44/10	57 (30~77)		GEM (250 mg/m^2 in 6 h d1, d8) + DDP (75 mg/m^2 d2)		
Zwitter M 2009[12]	RCT	125	95/30	58 (41~77)	NSCLC	GEM (1250 mg/m^2 in 30 min d1, d8) + DDP (75 mg/m^2 d2)	CRR PRR SDR PDR 1-YSR OS ORR PFS	N/A
		124	93/31	59 (40~79)		GEM (250 mg/m^2 in 6 h d1, d8) + DDP (75 mg/m^2 d2)		
Zwitter M, 2010[13]	RCT	57	46/11	66 (41–8)	NSCLC	GEM (1250 mg/m^2 in 30 min d1, d8) +DDP (60 mg/m^2 d2)	PFS CRR PRR OS ORR 1-YSR	N/A
		55	37/18	65 (49–80)		GEM (200 mg/m^2 in 6 h d1, d8) +DDP (60 mg/m^2 d2)		
Wu ZY 2014[14]	Non-RCT	37	28/9	58 (40–79)	NSCLC	Gem (250 mg/m^2 in 6 h d1, d8) + CBP (AUC 5 d1)	PFS ORR OS SDR	10
Narayanan P 2009[15]	Non-RCT	75	60/15	65(60–79)	NSCLC	Gem (350 mg/m^2 in 4 h d1, d8) + CBP (AUC 5 d1)	OS 1-YSR CRR PRR PDR ORR	8
Xiong J P 2008[16]	Non-RCT	58	39/19	61 (28–73)	NSCLC	Gem (250 mg/m^2 in 6 h d1, d8) + DDP (75 mg/m^2 d2)	ORR CRR PFS OS 1-YSR	11
Zwitter M 2005[17]	Non-RCT	32	22/10	58 (31–76)	NSCLC	Gem (250 mg/m^2 in 6 h d1, d8) + DDP (75 mg/m^2 d2)	ORR CRR PRR PFS OS 1-YSR	9
Kovac V 2012[18]	Non-RCT	78	58/20	58 (33–82)	MPM	Gem (250 mg/m^2 in 6 h d1, d8) + DDP (75 mg/m^2 d2)	CRR PRR SDR PDR PFS OS 1/ 2/3-YSR	11
Arrieta O 2014[19]	Non-RCT	39	26/13	59.7 (33–84)	MPM	Gem (250 mg/m^2 in 6 h d1, d8) + DDP (35 mg/m^2 d1, d8)	CRR PRR SDR PDR PFS OS	9
Khaled H 2008[20]	Non-RCT	57	41/16	55 (37–77)	Bladder cancer	Gem (250 mg/m^2 in 6 h d1, d8) + DDP (70 mg/m^2 d2)	CRR PRR PDR ORR PFS OS 1-YSR	10
Khaled H 2014[21]	RCT	60	48/12	62 (40–80)	Bladder cancer	Gem (1250 mg/m^2 in 30 min d1, d8)+DDP (70 mg/m^2 d2)	CRR PRR SDR PDR ORR PFS OS 1-YSR	N/A
		60	44/16	60 (40–85)		Gem (250 mg/m^2 in 6 h d1, d8) + DDP (70 mg/m^2 d2)		
Guan HH 2014[22]	Non-RCT	26	12/14	55 (46–71)	NPC	Gem (250 mg/m^2 in 6 h d1, d8) + NDP (80 mg/m^2 d1)	CRR PRR SDR PDR ORR PFS 1-YSR	8
Eckel F 2003[23]	Non-RCT	18	9/9	68 (51–81)	PC	Gem (100 mg/m^2 in 24 h d1, d8, d15)	PRR ORR PFS	6
Von DS 2005[24]	Non-RCT	19	8/11	63 (30–83)	GBC	Gem (100 mg/m^2 in 24 h d1, d8, d15)	PRR SDR PFS OS 1-YSR	7

(*Continued*)

Table 1 (Continued).

Trial	Study design	Patients	Male/ female	Age	Tumor type	Chemotherapy regimens	Endpoints assessed	MINORS Score
Schmid P 2005[25]	Non-RCT	44	0/44	45 (24–64)	Breast cancer	NPLD (60 mg/m^2 dl)+ DXT(60 mg/m^2 dl)+Gem (350 mg/m^2 in 4 h d4).	pCRR	9
Schmid P 1999[26]	Non-RCT	20	0/20	50.4 (35–63)	Breast cancer	Gem (250 mg/m^2 in 6 h dl, d8, d15)	CRR PRR ORR SDR PFS OS	8
Schmid P 2005[27]	Non-RCT	26	0/26	58.3 (32–75)	Breast cancer	Gem (350 mg/m^2 in 4 h dl, d8)+NVB (25 mg/m^2 dl, d8)	PRR ORR PFS OS	7
Spath SE 2000[28]	Non-RCT	18	10/8	58 (20–70)	STS	Gem (200 or 250 mg/m^2 in 6 h dl, d8, d15)	PRR SDR PFS 1-YSR	8

Abbreviations: ORR, overall response rate; SDR, stable disease rate; PDR, progressive disease rate; PRR, partial remission rate; CRR, complete remission rate; pCRR, pathologic complete response rate; CBP, carboplatin; DDP, cisplatin; NDP, nedaplatin; NPLD, non-pegylated; liposomal doxorubicin; DXT, docetaxel; MPM, malignant pleural mesothelioma; NPC, nasopharyngeal carcinoma; PC, pancreatic carcinoma; GBC, gallbladder and biliary tract carcinoma; STS, soft tissue sarcomas; RCT, randomized controlled trials.

addition, the functional, physical, and emotional roles, dyspnea, insomnia, and pain symptom scales were improved, and the most commonly graded 3/4 adverse effects were neutropenia (24.4%), lymphopenia (14.6%), thrombocytopenia (14.7%), and anemia (12.2%).

Bladder cancer

A phase II trial evaluated the efficacy and tolerability of a combination of Gem administered as P-LDI and cisplatin in patients with bladder cancer.[20] The ORR, complete remission (CR), and partial remission (PR) were 59.4%, 27%, and 50%, respectively. At a median observation time of 12 months, the PFS, OS, and 1-YSR were 7.2 months, 11.5 months, and 28%, respectively. Both hematological and non-hematological toxicities were treatable and not severe. The study suggested that Gem administered as P-LDI plus cisplatin is effective and safe for bladder cancer.

In a randomized phase II study,[21] 120 untreated patients with stage III/IV bladder cancer were randomized to receive either Gem in a 30-min SDI (arm 1) or Gem as P-LDI (arm 2), with the same dose of cisplatin. In 120 patients, the ORR, CR, PR, PFS, OS, and 1-YSR were 33.6% and 41.7%, 5% and 11.7%, 28.3% and 30%, 24 and 26 months, 16 and 12 months, and 54.7% and 49.9% in arms 1 and 2, respectively. The main toxicities were similar in both arms with no statistically significant differences. Accordingly, Gem administered as P-LDI in combination with cisplatin is an effective and well-tolerated regimen for patients with advanced bladder cancer.

Nasopharyngeal carcinoma

Guan[22] reported that Gem administered as P-LDI plus nedaplatin was effective in the treatment of metastatic nasopharyngeal carcinoma and yielded relatively mild side effects. In the study, the ORR, 1-YSR, and PFS were 80.7%, 57.7%, and 7.0 months, respectively. In addition, hematological toxicities were well tolerated, and the occurrence of grade I/II leukocytopenia and thrombocytopenia were 53.8% and 38.5%, respectively. Of note, grade III/IV leukocytopenia and thrombocytopenia were not observed.

Pancreatic carcinoma

In a phase II trial,[23] 18 patients with advanced pancreatic carcinoma were treated with Gem (100 mg/m^2) infused over 24 h on days 1, 8, and 15. All patients were assessable for

Table 2 Quality evaluation of included RCTs

Included trials	Sequence generation	Allocation concealment	Blinding	Incomplete data	Selective reporting	Other sources of bias
Beniwal SK, 2012[10]	Unclear	Unclear	Unclear	No	Unclear	Unclear
Vrankar M, 2014[11]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Zwitter M, 2009[12]	Computer-generated sequence of random numbers	Unclear	Single-blind	Yes	Unclear	Unclear
Zwitter M, 2010[13]	Computer-generated sequence of random numbers	Unclear	Single-blind	Yes	Unclear	Unclear
Khaled H 2014[21]	Unclear	Unclear	Unclear	No	Unclear	Unclear

Abbreviation: RCTs, randomized controlled trials.

therapeutic response. Of note, grade 3 neutropenia and thrombocytopenia occurred in 1 patient each. The median PFS was 4.4 months, ORR was 16.7%, and the symptom and quality-of-life scores were improved. The study suggested that patients might benefit from 24-h Gem.

Gallbladder and biliary tract carcinoma

Based on a phase I study in patients with NSCLC, Von[24] conducted a phase II trial of weekly 24-h infusion of Gem in patients with advanced gallbladder and biliary tract carcinoma (GBC). In the study, 18 patients were evaluable for response. The 1-YSR, PFS, and OS were 34%, 3.6 months, and 7.5 months, respectively. Notably, toxicities were mild. Hence, 24-h infusion of Gem at a low dose is effective and safe for the treatment of GBC.

Breast cancer

Based on a phase II study conducted by Schmid,[25] 44 patients with stage II/III breast cancer were treated with NPLD (60 mg/m^2, d1), docetaxel (75 mg/m^2, d1), and Gem (350 mg/m^2 in 4-h infusion, d4). The treatment was repeated every 21 days for a maximum of six cycles. The ORR was 80%, and the tumor diameter decreased from 3.5 cm to 1.4 cm. In addition, breast conservation surgery was performed in 19 patients with an initial tumor size <3 cm and 14 patients with tumor size ≥3 cm. Moreover, modified mastectomies were performed for the remaining patients. The toxicity of the regimen was moderate. Overall, this modified chemotherapy regimen was a highly active and safe regimen for primary chemotherapy in patients with breast cancer, which corroborated the previous study.

Another phase II study of Gem administered as prolonged infusion plus vinorelbine in anthracycline and/or taxane-pretreated metastatic breast cancer reported that the ORR, PFS, and OS were 30.4%, 4.6 months, and 14.5 months, respectively.[26] Notably, hematological and non-hematological toxicities were generally moderate. Hence, this regimen represented a therapeutic option for patients receiving second-line therapy for metastatic breast cancer.

Soft tissue sarcomas

In a phase II study of Gem in patients with pretreated advanced soft tissue sarcomas,[28] the initial dose of Gem was 200 mg/m^2. The dose escalation to 250 mg/m^2 was allowed in the case of SD with well tolerated. Overall, 2 patients had PR and 6 had SD for 3–6 months. The median OS was 8 months. The treatment was generally well tolerated and with no treatment-related death.

Discussion and future perspectives

As mentioned earlier, DK is saturated at concentrations of 10–20 μmol/L of Gem. The reaction rate is constant at higher concentrations.[29] Hence, the MTD and toxicity profile closely depend on the infusion time. In a phase I trial, Pollera[6] investigated the maximum tolerated infusion time (MIIT) of prolonged infusion for Gem and reported that the MIIT of the 875 mg/m^2 group was 1 h and that of the 300 mg/m^2 group was 6 h. In addition, a phase I trial conducted by Schmid[4] reported that when Gem was administered as a 4-h infusion, the MTD was 400 mg/m^2, and dose-limiting toxicities (DLTs) were neutropenia, thrombocytopenia, stomatitis, and elevation of liver enzymes. Another phase I study evaluated the MTD of Gem administered as a 3-h infusion.[7] The MTD was

Table 3 Clinical application of Gem given in P-LDI

Trials	Tumor types	patients	Administration of GEM P-LDI or 30-min SDI	outcomes				Conclusions
				PFS month	OS month	ORR %	1-YSR %	
Beniwal SK 2012[10]	NSCLC	30	30-min SDI	5.5	9.7	40	33.7	P-LDI has an equal activity and low toxicity compared with 30-min SDI.
		30	P-LDI	5.4	10.7	36.6	36.6	
Vrankar M 2014[11]	NSCLC	52	30-min SDI	15.7	24.8	61.5	73.1	A trend towards better efficacy of treatment with P-LDI, but no statistical significance difference. Both schedules had a comparable toxicity profile.
		54	P-LDI	18.9	28.6	61.1	81.5	
Zwitter M 2009[12]	NSCLC	125	30-min SDI	5.5	10.1	32.8	46.6	P-LDI has an equal activity and low toxicity compared with 30-min SDI.
		124	P-LDI	6.0	10.0	46.8	41.1	
Zwitter M 2010[13]	NSCLC	57	30-min SDI	3.8	4.3	8.8	8.8	P-LDI has very low toxicity and better efficacy compared with 30-min SDI.
		55	P-LDI	5.6	6.8	25.5	25.5	
Wu ZY 2014[14]	NSCLC	37	P-LDI	7.0	14.0	62.2	N/A	Gem in P-LDI combined with CBP was efficacious in patients with well tolerated toxicity profiles.
Narayanan P 2009[15]	NSCLC	75	P-LDI	N/A	11	25.3	40	Gem in P-LDI combined with CBP was effective in advanced NSCLC, and its toxicity was very favorable.
Xiong J P 2008[16]	NSCLC	58	P-LDI	5.5	10.5	39.3	41.4	Gem in P-LDI plus DDP was effective in NSCLC treatment. Toxicity, especially myelosuppression, was remarkably mild.
Zwitter M 2005[17]	NSCLC	32	P-LDI	6	9.5	43.8	40	treatment with Gem in P-LDI plus DDP was feasible.
Kovac V 2012[18]	MPM	78	P-LDI	8	17	50	67.3	Gem in P-LDI plus DDP may be considered for the primary treatment of MPM, especially in economically deprived populations.
Arrieta O 2014[19]	MPM	39	P-LDI	6.9	20.7	53.8	N/A	Gem in P-LDI plus DDP showed acceptable toxicity and high efficacy with improvement in the quality of life, representing an affordable regimen for the low-income population.
Khaled H 2008[20]	Bladder cancer	57	P-LDI	7.2	11.5	59.4	28	Gem in P-LDI plus DDP was an effective treatment for advanced bladder cancer. Toxicity, especially myelosuppression, was surprisingly mild.
Khaled H 2014[21]	Bladder cancer	60	30-min SDI	24	16	33.3	54.7	Gem in P-LDI plus DDP was not inferior to the standard GC regimen with a favorable toxicity profile and less financial costs.
		60	P-LDI	26	12	41.7	49.9	

(*Continued*)

Table 3 (Continued).

Trials	Tumor types	patients	Administration of GEM P-LDI or 30-min SDI	outcomes				Conclusions
				PFS month	OS month	ORR %	1-YSR %	
Guan HH 2014[22]	NPC	26	P-LDI	7	N/A	80.8	58	Gem in P-LDI plus nedaplatin was effective for nasopharyngeal carcinoma and yielded relatively mild toxicities.
Eckel F 2003[23]	PC	18	P-LDI	4.4	N/A	16.7	N/A	Gem in P-LDI seems to be as active as the 30 min-SDI. Relatively long PFS and improvement of symptom and quality of life scores.
Von DS 2005[24]	GBC	19	P-LDI	3.6	7.5	6	34	24 hr Gem at a dose of 100 mg/m^2 was well tolerated, relatively high rate of disease control.
Schmid P 2005[25]	Breast cancer	44	P-LDI	N/A	N/A	80	N/A	The evaluated schedule provides a safe and highly effective combination treatment for patients with early breast cancer.
Schmid P 1999[26]	Breast cancer	20	P-LDI	6.3	51.9	25	N/A	Gem in P-LDI plus vinorelbine was an effective treatment in metastatic breast cancer.
Schmid P 2005[27]	Breast cancer	26	P-LDI	4.6	14.5	30.4	N/A	Gem in P-LDI plus vinorelbine was a safe and effective treatment in anthracycline and/or taxane pretreated patients.
Späth SE 2000[28]	STS	18	P-LDI	N/A	8	11	28	Gem in P-LDI has a favorable toxicity profile and displays antitumor activity in patients with pretreated advanced soft tissue sarcomas.

Abbreviations: N/A, unknown or not measured; MPM, malignant pleural mesothelioma; NPC, nasopharyngeal carcinoma; PC, Pancreatic carcinoma; GBC, gallbladder and biliary tract carcinoma; STS, Soft tissue sarcomas.

defined as 450 mg/m^2, with myelosuppression and asthenia being DLTs. Moreover, Anderson[8] conducted a phase I study to evaluate the MTD of Gem administered as a 24-h infusion; the dose levels were 10, 20, 40, 80, 120, 180, and 210 mg/m^2, and the MTD was 180 mg/m^2, with neutropenia and lethargy as DLTs. Based on the previous studies, the MTD of Gem is heavily dependent on the infusion time. When the infusion time of 3 h, the MTD is 450 mg/m^2, and when the infusion time increases to 4, 6, and 24 h, the MTD decreases to 400, 300, and 180 mg/m^2, respectively. Hence, dosage and infusion time should be considered when Gem is administered as a prolonged infusion.

Although a pharmacological advantage is attained by prolonging the infusion time, the clinical efficacy of P-LDI is not superior to 30-min SDI in various clinical studies, which could be associated with genetic polymorphism. Notably, genetic polymorphism could result in different expressions of DK, cellular transporter, and cytidine deaminase from person to person, which could contribute to individual variability in Gem pharmacokinetics and toxicity.[30,31] Hence, it is imperative to consider both infusion time and genotype in optimizing the Gem triphosphate accumulation.

Disclosure

The authors report no conflicts of interest in this work.

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