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ORIGINAL ARTICLE

Comparison of Different Gemcitabine Formulations Regarding Cost-analysis and Duration of Exposure

Metin Deniz KARAKOÇ

Department of Medical Pharmacology, Pamukkale University Faculty of Medicine, Denizli-*Türkiye*

OBJECTIVE

Gemcitabine, a widely used chemotherapeutic agent, is available in two pharmaceutical formulations: Lyophilized powder (LP) and concentrated liquid (CL). The preparation periods and costs of wasted doses differ significantly, impacting both healthcare expenditures and occupational safety. This study aimed to compare the cost analysis and personnel exposure duration associated with these drugs.

METHODS

A single-center observational analysis was conducted. Preparation periods for the LP and CL formulations of gemcitabine were recorded over one year. Additionally, the quantities of wasted doses and their associated costs were documented daily.

RESULTS

Annually, 2.26% (41,010 mg) of gemcitabine was wasted, irrespective of the formulation. The waste rate was 4.40% for LP formulations and 0.36% for CL formulations ($p<0.0001$). The annual cost of wasted drugs was significantly higher for LP formulations compared to CL formulations ($p<0.0001$). If all gemcitabine infusion solutions were prepared using CL-form drugs, an estimated annual cost savings of $1,394.79 (84%) could be achieved compared to current practices. The use of ready-to-use CL-form drugs that eliminate the need for reconstitution enabled a 2.8-fold reduction in preparation time and resulted in an estimated 18.5-hour annual reduction in exposure duration.

CONCLUSION

Switching to CL-form gemcitabine could be a practical strategy to enhance cost savings and reduce occupational exposure in chemotherapy preparation. Further multi-center studies are warranted to confirm the generalizability of these findings.

Keywords: Gemcitabine; occupational exposure; pharmacoeconomics; rational drug use.

INTRODUCTION

Cancer is a significant public health concern with a rising incidence in recent years, ranking among the leading causes of death worldwide. The disease not only affects individual health but also imposes substantial economic and societal burdens. Despite advancements in treatment strategies such as immunotherapy, targeted therapies, and cancer vaccines, conventional chemotherapy with cytotoxic drugs remains the most widely used approach for cancer treatment.[1] Among these agents, gemcitabine is extensively utilized for treating

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Dr. Metin Deniz KARAKOÇ
Pamukkale Üniversitesi Tıp Fakültesi,
Tıbbi Farmakoloji Anabilim Dalı,
Denizli-Türkiye
E-mail: mdkarakoc@pau.edu.tr

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various cancers, including pancreatic, ovarian, lung, bladder, and breast cancers. It can be administered either as monotherapy or as part of a combination chemotherapy protocol. As an antimetabolite, gemcitabine targets the S phase of the cell cycle and inhibits DNA synthesis. However, like other cytotoxic agents, gemcitabine exhibits non-specific toxicity, affecting healthy cells in addition to tumor cells. Its toxicity is influenced by various factors, including intrinsic carcinogenic properties, tissue concentrations, and the duration of exposure.[2,3] In healthy individuals, such as healthcare personnel, repeated exposure to cytotoxic agens can result in both acute and chronic toxic effects. Notable side effects include toxicity to the kidneys, liver, heart, lungs, hematopoietic and reproductive systems, as well as ototoxicity, immunotoxicity, dermal toxicity, and teratogenic and carcinogenic effects.[4,5]

Gemcitabine is typically administered as a 30-minute intravenous infusion in 250 or 500 mL of 0.9% NaCl (physiological saline) at a dose of 1000–1250 mg/m^2. It is available in two pharmaceutical forms: Concentrated liquid (CL) and lyophilized powder (LP). Both forms contain equivalent doses of gemcitabine and provide the same therapeutic effects.[6] However, they differ in cost, stability of remaining doses after vial opening, and the preparation time required by healthcare staff. The LP form is relatively less expensive to transport and has a lower risk of breakage and spillage. However, once reconstituted, any remaining dose must be used within 24 hours, which poses an economic disadvantage. In contrast, the CL form is ready-to-use and offers greater convenience for drug preparation. When accessed using closed-system chemotherapy transfer devices, the remaining doses can remain stable for up to seven days under validated aseptic clean room conditions.[7] Despite these advantages, the CL form has a higher risk of breakage and spillage during transport and storage due to its heavier weight compared to the LP form. Therefore, this study aimed to compare the two formulations of gemcitabine in terms of cost-benefit and preparation time. Evaluating these parameters may help reduce drug waste costs and promote a safer working environment for healthcare professionals handling cytotoxic agents.

MATERIALS AND METHODS

This study was conducted as an analytical research project with written approval from the Non-interventional Clinical Research Ethics Committee of Pamukkale University (Approval No: 25.01.2024-E.481626, Date: 25/01/2024). No interventional procedures, additional treatments, treatment modifications, tests, or biological material sampling were performed on healthy volunteers or cancer patients. The study is conducted according to the Helsinki Declaration.

Data collection and Processing Procedure

The preparation times of infusion solutions (CL and LP formulations) for gemcitabine-containing medications at the Denizli Public Hospital Cancer Diagnosis and Treatment Center were recorded between February 1, 2024, and January 31, 2025. Additionally, any remaining waste medication at the end of each day was documented. The costs associated with the wasted amounts of these pharmaceutical forms over the study period were compared. The exposure time of chemotherapy preparation personnel to cytotoxic drugs was calculated as the duration from when the drug and serum were placed in the passbox of the chemotherapy preparation cabinet to when the prepared infusion solution was removed from the passbox. The CL and LP drug forms were never mixed within the same infusion solution. Drug preparation and timing measurements were conducted by the same personnel, who were not the authors of the study and declared no conflicts of interest with the authors. The selection of the pharmaceutical form used in the study was carried out in a fully randomized manner by physicians who were not authors of the study and had no conflict of interest with the author. Drug prices were calculated using the retail prices determined by the Republic of Türkiye Ministry of Health. Prices in Turkish Lira were converted to United States Dollars (USD) based on exchange rates published by the Central Bank of the Republic of Türkiye.

Statistical Analysis

Statistical analyses were performed using SPSS 29.0 (SPSS Inc., Chicago, IL, USA). Data were presented as descriptive statistics (mean, range, and percentage). The Shapiro–Wilk test was used to evaluate the distribution of the data, and Levene's test assessed the homogeneity of variance. Both tests indicated that the data were not suitable for an independent samples t-test. Therefore, the statistical relationship between the two forms was analyzed using the Mann-Whitney U test, the non-parametric equivalent of the independent samples t-test. A p-value of <0.05 was considered significant.

RESULTS

No significant difference in the mean price was observed between the two forms (CL: 0.0426 USD/mg;

Table 1 Distribution of gemcitabine consumption and cost of wasted doses

Month/ year	Form of drug	Number of patients	Number of prepared infusion solutions	Total dosage of used vials (mg)	Total cost (USD)	Wasted dosage (mg) and ratio (%)		Cost of wasted doses (USD)
02.24	LP	17	44	60.550	2.294,56	2.450	4.05	93.49
	CL	21	50	70.440	2.688,07	300	0.43	11.37
03.24	LP	18	47	65.830	2.399,14	2.570	3.90	94.32
	CL	22	59	81.590	2.943,88	410	0.50	14.94
04.24	LP	19	54	74.540	2.689,51	2.210	2.96	80.30
	CL	22	61	85.310	3.082,58	170	0.20	6.13
05.24	LP	19	57	78.820	2.848,07	3.140	3.98	114.26
	CL	22	58	80.250	2.875,19	230	0.29	8.31
06.24	LP	20	58	81.040	2.903,50	4.050	5.00	146.12
	CL	23	61	84.740	3.774,82	360	0.42	12.90
07.24	LP	20	58	80.750	3.597,08	3.740	4.63	167.54
	CL	23	61	84.350	3.676,56	350	0.41	15.59
08.24	LP	19	54	74.610	3.252,02	3.120	4.18	136.76
	CL	22	60	83.320	3.590,09	200	0.24	8.72
09.24	LP	19	50	69.600	2.998,92	2.800	4.02	121.33
	CL	22	60	83.220	3.563,89	240	0.29	10.34
10.24	LP	18	49	67.580	2.894,10	3.140	4.65	135.23
	CL	22	58	80.220	3.366,44	290	0.36	12.42
11.24	LP	18	48	66.110	2.774,31	3.430	5.19	144.75
	CL	22	57	77.990	3.232,81	350	0.45	14.69
12.24	LP	18	49	67.550	2.800,05	3.750	5.55	156.32
	CL	21	56	77.330	3.223,50	270	0.35	11.19
01.25	LP	18	48	66.510	2.791,10	3.180	4.78	132.56
	CL	20	54	74.730	3.097,67	260	0.35	10.78
Monthly mean	LP	18.6	51.33	71,124.2	2,853.53	3,131.67[a]	4.40	126.92[a]
	CL	21.8	57.92	80,290.8	3,259.63	285.83[b]	0.36	11.45[b]
Total	485	1311	1,816,980	73,357.87	41.010	2.26	1,660.35	

[a,b]: Different superscript letters in the same column indicate statistical difference ($p<0.0001$). USD: United States dollar; LP: Lyophilized powder form; CL: Concentrated liquid form

LP: 0.0429 USD/mg). The study determined that 4.40% of drugs in the LP form and 0.36% of drugs in the CL form were wasted because they could not be used within the stability period after vial seal opening. The difference in wasted amounts between the two pharmaceutical forms was found to be significant ($p<0.0001$). Consequently, the annual cost of wasted drugs was significantly higher for the LP form (1,522.98 USD) compared to the CL form (137.38 USD) ($p<0.0001$). Data on the annual gemcitabine usage in the chemotherapy unit are presented in Table 1.

During the study period, 109 gemcitabine-containing infusion solutions were prepared monthly for an average of 40 patients. In all chemotherapy protocols, a gemcitabine dose of 1000 mg/m² was administered either as monotherapy or as part of combination therapy, given three times within 28 days or twice within 21 days. The average dose administered per patient was 1354.7 mg. Table 2 presents data on the preparation times for LP and CL forms of the drug in the cytotoxic drug preparation cabinet. Annually, approximately 2.26% (41,010 mg) of gemcitabine was wasted, regardless of the pharmaceutical form. However, waste from LP-form drugs, which have significantly shorter stability after reconstitution, was found to be 12-fold higher than that of CL-form drugs. If all gemcitabine infusion solutions were prepared using CL-form drugs, the estimated annual waste dose cost would be 265.56 USD, representing a savings of 1,394.79 USD (84%) compared to the current practice.

A significant difference in personnel exposure was observed between the two pharmaceutical forms during infusion solution preparation (LP form: 3.03 minutes, CL form: 1.08 minutes; $p<0.0001$). Choosing

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Table 2 Duration of preparation for different pharmaceutical forms of gemcitabine in cytotoxic drug preparation cabinet

Month/ year	Form of drug	Number of prepared gemcitabine infusion solutions	Mean duration of preparation (min)			Total duration (min)
02.24	LP	44	3.10			136.4
	CL	50	1.00			50.0
03.24	LP	47	3.10			145.7
	CL	59	1.10			64.9
04.24	LP	54	3.00			162.0
	CL	61	1.00			61.0
05.24	LP	57	3.00			171.0
	CL	58	1.10			63.8
06.24	LP	58	3.00			174.0
	CL	61	1.10			67.1
07.24	LP	58	2.90			168.2
	CL	61	1.00			61.0
08.24	LP	54	2.90			156.6
	CL	60	1.10			66.0
09.24	LP	50	3.00			150.0
	CL	60	1.00			60.0
10.24	LP	49	3.10			151.9
	CL	58	1.10			63.8
11.24	LP	48	3.00			144.0
	CL	57	1.20			68.4
12.24	LP	49	3.10			151.9
	CL	56	1.10			61.6
01.25	LP	48	3.10			148.8
	CL	54	1.10			59.4
Mean	LP	51.3	3.03[a]	Total	LP	1860.5[a]
	CL	57.9	1.08[b]		CL	747[b]

[a,b]: Different superscript letters in the same column indicate statistical difference ($p<0.0001$). LP: Lyophilized powder form; CL: Concentrated solution form

the LP form over the CL form for gemcitabine administration increases healthcare personnel's exposure to the cytotoxic drug by approximately 2.8-fold due to the longer preparation time.

DISCUSSION

The incidence of cancer has been steadily rising in recent decades, both globally and in our country. Although various treatment modalities are available—including radiotherapy, surgery, and targeted therapies such as checkpoint inhibitors, tyrosine kinase inhibitors, and monoclonal antibodies—conventional chemotherapy with cytotoxic drugs, such as gemcitabine, remains the most widely used treatment option.[8] However, the preparation and disposal of cytotoxic drugs pose significant risks, including spills, dispersion, and airborne contamination. These risks threaten both patient and worker safety and also contribute to environmental pollution.[9] To mitigate these harmful effects, most hospitals providing chemotherapy services prepare cytotoxic drugs under validated aseptic conditions. These preparations are carried out in negative-pressure clean rooms equipped with Class IIB2 biological safety cabinets. Additionally, needle-free, closed-system vial transfer devices are used to enhance safety and minimize contamination.[10,11]

Despite stringent safety measures, numerous studies have shown that healthcare workers remain exposed to low levels of cytotoxic contaminants. Even with detailed guidelines and regulations in place, personnel involved in cytotoxic drug preparation—including nurses, pharmacists, and laboratory technicians—are still at risk of hazardous substance exposure. Studies have highlighted the inconsistent implementation of these guidelines, which undermines their overall effectiveness.[9–12] Evidence of early DNA damage in healthcare workers handling antineoplastic drugs has

been documented. Reported cytogenetic effects include mutagenic activity in the urinary system, chromosomal abnormalities, micronucleus induction, and chromatid exchanges.[5,13,14] Furthermore, epidemiological studies have linked exposure to hazardous drugs with both acute and long-term health outcomes, including infertility, miscarriages, stillbirths, and cancer.[15] These findings underscore the urgent need to develop and enforce more effective strategies to further reduce exposure among healthcare workers.

In our country, hospitals offering chemotherapy services are required to procure antineoplastic drugs. Gemcitabine is available in multiple dosage forms, including 200 mg, 1000 mg, 1400 mg, and 2000 mg, and is marketed in two formulations: CL and LP.[16] During public procurement processes, the selection is based on the lowest bid for each dosage form. As a result, the 200 mg dosage may come as a CL formulation from one manufacturer, while the 1000 mg dosage may be an LP formulation from another. Variations in excipients between these formulations can lead to significant differences in adverse effects, even for products from the same pharmaceutical company. Mixing CL and LP formulations for chemotherapy infusions poses a risk of severe allergic complications in patients. To ensure patient safety, drugs with the same active ingredient but different formulations must not be combined. This issue presents substantial challenges, including increased stock costs, difficulties in managing waste doses requiring disposal, and heightened occupational exposure to cytotoxic agents for drug preparation personnel. For the unused portion of an opened vial to be used for another patient, the drug must retain its physical, chemical, and microbiological stability.[17,18] Generally, CL formulations have shorter shelf lives (15–24 months) compared to LP formulations and carry additional disadvantages, such as greater transport weight and an increased risk of breakage and spillage during transit. Once opened, remaining doses in CL vials can maintain stability for up to seven days under validated, aseptic clean room conditions when handled with closed-system chemotherapy transfer devices. In contrast, LP formulations must be used within 24 hours after reconstitution.[7] These complexities necessitate the adoption of rational policies and the selection of drugs that are both cost-effective and minimize personnel exposure.

The widespread use of gemcitabine makes it one of the drugs most commonly associated with contamination during preparation. A study conducted in Spain identified gemcitabine, along with 5-fluorouracil and cyclophosphamide, as one of the most frequently detected contaminants on work surfaces.[19] Similarly, a multicenter study in Italy reported that gemcitabine, cyclophosphamide, and ifosfamide were the most commonly contaminated antineoplastic agents across all working areas. However, it was noted that no detectable levels of antineoplastic drug residues were found in urine samples collected from pharmacists and nurses.[20] While closed-system transfer devices significantly reduce surface contamination, they cannot completely eliminate it. Measures to minimize the time personnel spend handling antineoplastic drugs can further mitigate potential harmful effects. Numerous studies have examined surface contamination and personnel exposure by analyzing blood and urine samples from work environments and staff involved in cytotoxic drug preparation.[13,14,21] Although many studies have demonstrated antineoplastic contamination in work areas and personnel exposure, these studies offer no solution beyond recommending stricter adherence to safety standards. Conversely, our study suggests a novel approach to mitigating personnel exposure. Specifically, CL formulations were found to significantly shorten preparation times compared to LP formulations, reducing the duration personnel spend inside the preparation cabinet. Using ready-to-use CL-formulations that simplify preparation procedures enabled staff to complete tasks significantly faster and decreased cumulative annual exposure duration. The LP and CL formulations of gemcitabine exhibit similar pharmacokinetic and pharmacodynamic profiles. The route of administration and infusion durations are identical for both formulations, and to our knowledge, no study in the literature has reported any significant difference between them regarding adverse effects. Since both drugs are administered via infusion in isotonic sodium chloride, there is no notable difference in the risk of preparation or administration errors. However, the CL formulation contains hydrochloric acid, sodium hydroxide, and water for injection as excipients. In contrast, the LP formulation additionally includes mannitol and sodium acetate. Due to the presence of these additional substances, the possibility of reduced tolerability or an increased risk of allergic reactions in sensitive individuals should not be overlooked.

Rational drug use and reducing wasted dose costs are essential for maintaining a sustainable healthcare reimbursement system. As of 2024, the global antineoplastic drug market is valued at approximately 220 billion USD and is projected to grow to 409 billion USD by 2028. Healthcare systems increasingly face challeng-

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es related to reimbursement and access to systemic oncology drugs, resulting in a widening gap between the price, affordability, and clinical value of antineoplastic therapies worldwide. To address these issues and ensure future access to medicines, cost-effectiveness and cost-saving studies have become more critical than ever.[22,23] Türkiye reflects the global trend, with a continuous rise in both the volume of antineoplastic drugs consumed and associated expenditures in recent years.[24] Reducing discarded doses of antineoplastic drugs presents a significant opportunity for cost savings.[25] Several solutions have been proposed in previous studies, including using closed-system chemotherapy equipment, selecting dosage forms that align with daily unit needs instead of utilizing all available formulations of a cytotoxic drug, and centralizing chemotherapy preparation for multiple hospitals to minimize wasted doses.[26–28] Our study found that gemcitabine was wasted at an average rate of 2.26% per year, irrespective of the pharmaceutical form. However, wasted doses generated by LP-formulations were 12 times higher than those of CL-formulations. Transitioning to CL formulations could reduce annual waste costs by 84%, yielding savings of 1,394.79 USD. According to the latest Ministry of Health data, there are 1,555 hospitals in Türkiye, but only around 500 are capable of providing specialized services such as chemotherapy.[24] While the initial savings may seem modest compared to the national cancer drug budget, implementing this approach across all chemotherapy-administering centers in Türkiye could save approximately 700,000 USD annually and significantly reduce healthcare staff exposure to cytotoxic drugs. In our study, no significant difference was found between the drug formulations in terms of purchasing costs. However, the CL formulations provided a substantial financial advantage over the LP formulations in terms of waste dose costs. Since both formulations require a vial adapter, a transfer set, and an infusion bag for preparation, there is no difference between them regarding the consumption of closed-system medical supplies. On the other hand, the preparation time for CL formulations is shorter than that for LP formulations. This leads to faster delivery of care to patients, reduces personnel exposure time to cytotoxic substances, and consequently decreases workload. It was demonstrated that switching the formulation of a single drug could indirectly save approximately 18.5 hours of personnel costs annually.

Gemcitabine is one of 63 licensed active substances that are administered parenterally and prepared in chemotherapy cabinets in our country. Additionally, 41 other active substances are also administered parenterally; however, these are not locally licensed and are imported with special authorization for specific indications.[29] The findings of this study suggest that similar strategies could be applied to other drugs, where feasible, to enhance cost savings and reduce personnel exposure. Nevertheless, as this study was conducted at a single center, its results may not be generalizable to the national level. This constitutes a limitation of the study.

CONCLUSION

This study suggests that switching from LP preparations to CL forms of gemcitabine may provide notable advantages in terms of cost-effectiveness and occupational safety. The use of CL forms reduces wasted dose costs and shortens the duration of personnel exposure to cytotoxic agents during drug preparation. However, further multi-center studies are necessary to confirm these findings and assess their generalizability.

Ethics Committee Approval: The study was approved by the Pamukkale University Non-interventional Clinical Research Ethics Committee (no: E.481626, date: 25/01/2024).

Informed Consent: Informed consent was obtained from all participants.

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