Stability of Captisol-enabled versus propylene glycol–based melphalan at room temperature and after refrigeration

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Purpose. To compare the chemical stability of Captisol-enabled (CE) melphalan ("CE-melphalan"; Evomela, Acrotech Biopharma LLC) and propylene glycol (PG)–based melphalan ("PG-melphalan"; Alkeran, GlaxoSmithKline) admixtures prepared with 0.9% sodium chloride injection in polyvinyl chloride (PVC) bags or reconstituted vials stored at room temperature (RT) and under refrigeration.

Methods. Lyophilized CE-melphalan and generic PG-melphalan were reconstituted to 5 mg/mL with 0.9% sodium chloride injection or manufacturer-supplied diluent, respectively. The reconstituted vials were then diluted to the desired concentrations with 0.9% sodium chloride injection in PVC bags and were stored at RT (23°C) or under refrigeration (4°C). Aliquots were withdrawn from the bags and reconstituted vials of CE-melphalan and PG-melphalan immediately after preparation and at predetermined time intervals. Melphalan concentrations were measured using a validated high-performance liquid chromatography method.

Results. CE-melphalan reconstituted in PVC bags at concentrations of 1 and 2 mg/mL was stable for 6 and 24 hours, respectively, at RT and for 8 and 24 hours, respectively, at 4°C. PG-melphalan reconstituted in bags at 1, 1.5, and 2 mg/mL was stable for 1, 2, and 2 hours, respectively, at RT and for 2, 4, and 4 hours, respectively, at 4°C. Reconstituted CE-melphalan vials were stable for 48 hours at both RT and 4°C, whereas PG-melphalan vials were stable for 6 hours at RT but formed precipitate within 2 hours at 4°C.

Conclusion. CE-melphalan remained stable longer than generic PG-melphalan under the test conditions. CE-melphalan at 2 mg/mL has 24-hour stability at RT and can be used for extended infusion times or may be compounded ahead of time. Reconstituted CE-melphalan vials are stable for 48 hours at both RT and 4°C.

Keywords: Alkeran, Captisol-enabled melphalan, drug stability, Evomela, hematopoietic stem cell transplantation, propylene-glycol melphalan

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The alkylating agent melphalan is regularly used in conditioning regimens for both autologous and allogenic hematopoietic stem cell transplantation because of its broad antitumor activity, ability to ablate the bone marrow, minimal extramedullary toxicity, and potent immunosuppressive effects.[1-5] Previous research found that an increased duration of melphalan exposure (5-6 hours) results in a 3-fold higher intracellular concentration without saturating the uptake transporters.[6] The researchers concluded that continuous exposure to melphalan for a longer duration might improve treatment outcomes. This evidence strongly supports the investigation of a continuous infusion of melphalan for longer duration; however, such an investigation cannot be accomplished

with a melphalan formulation that rapidly degrades after reconstitution.[7]

The US Food and Drug Administration has approved 2 melphalan formulations. The older and most often used formulation, propylene glycol (PG)–based melphalan, or "PG-melphalan" (Alkeran; GlaxoSmithKline), uses PG as an excipient. This formulation is highly unstable in aqueous solution, has a short stability duration (60 minutes per the package insert), and cannot be used for long infusions.[8] In addition, PG causes renal and cardiac toxicities.[1] The other, newer formulation, Captisol-enabled (CE) melphalan (Evomela; Acrotech Biopharma), or "CE-melphalan," is an intravenous (IV) formulation that uses Captisol (sulfobutylether-β-cyclodextrin; Ligand Pharmaceuticals) as the solubilizing and stabilizing agent. CE-melphalan remains stable longer than PG-melphalan does, and its excipient has no known toxicities.

CE-melphalan in IV solution at room temperature (RT; 23°C) is stable for 4 hours.[9] Singh et al[10] recently showed that the solution can remain stable for up to 11 hours at RT when stored in small vials; however, the reported data does not represent the actual admixtures, which are prepared in polyvinyl chloride (PVC) bags. Previous studies have shown that IV admixture stability varies depending on whether the admixture is stored in glass versus PVC bags.[11,12] There are no published stability data for CE-melphalan admixtures prepared in 0.9% sodium chloride injection in PVC bags and stored for more than 4 hours for patient use in hospitals, even though stability beyond 4 hours is, in general, required to allow adequate time for pharmacy preparation and distribution. Of note, administration of melphalan over an extended time cannot be investigated with a formulation that degrades rapidly.

It is currently unclear for how long CE- and PG-melphalan formulations are stable at RT and under refrigeration (4 °C) after the drugs have been reconstituted for infusion. It is also unclear how these 2 formulations compare in terms of their degradation when they are kept under the conditions required for patient administration. Accordingly, in this study, we investigated and compared the extended stability of CE- and PG-melphalan when the drugs were stored under different conditions and for different durations appropriate for patient care.

KEY POINTS

- Intravenous (IV) admixtures of Captisol-enabled melphalan at a concentration of 2 mg/mL prepared with 0.9% sodium chloride injection in PVC bags are chemically and physically stable for 24 hours when refrigerated or stored at room temperature.
- IV admixtures of propylene glycol–based melphalan at concentrations of 1.5 and 2 mg/mL prepared with 0.9% sodium chloride in PVC bags are chemically and physically stable for 4 hours when refrigerated or 2 hours when stored at room temperature.
- These new extended-stability data may benefit pharmacy operations, reduce waste, and improve treatment outcomes in transplantation patients.

Materials and methods

Chemicals and reagents. Melphalan reference standard was purchased from TLC Pharmaceutical Standards, Newmarket, ON, Canada.[a] All solvents were of high-performance liquid chromatography grade or higher purity and were purchased from Fisher Scientific.[b] CE-melphalan (Evomela) was provided by Spectrum Pharmaceuticals/Acrotech Biopharma.[c] Generic PG-melphalan (Mylan),[d] glass vials, and 50- and 25-mL PVC bags (Baxter Healthcare) containing 0.9% sodium chloride injection[e] were obtained from The University of Texas MD Anderson Cancer Center's Division of Pharmacy.

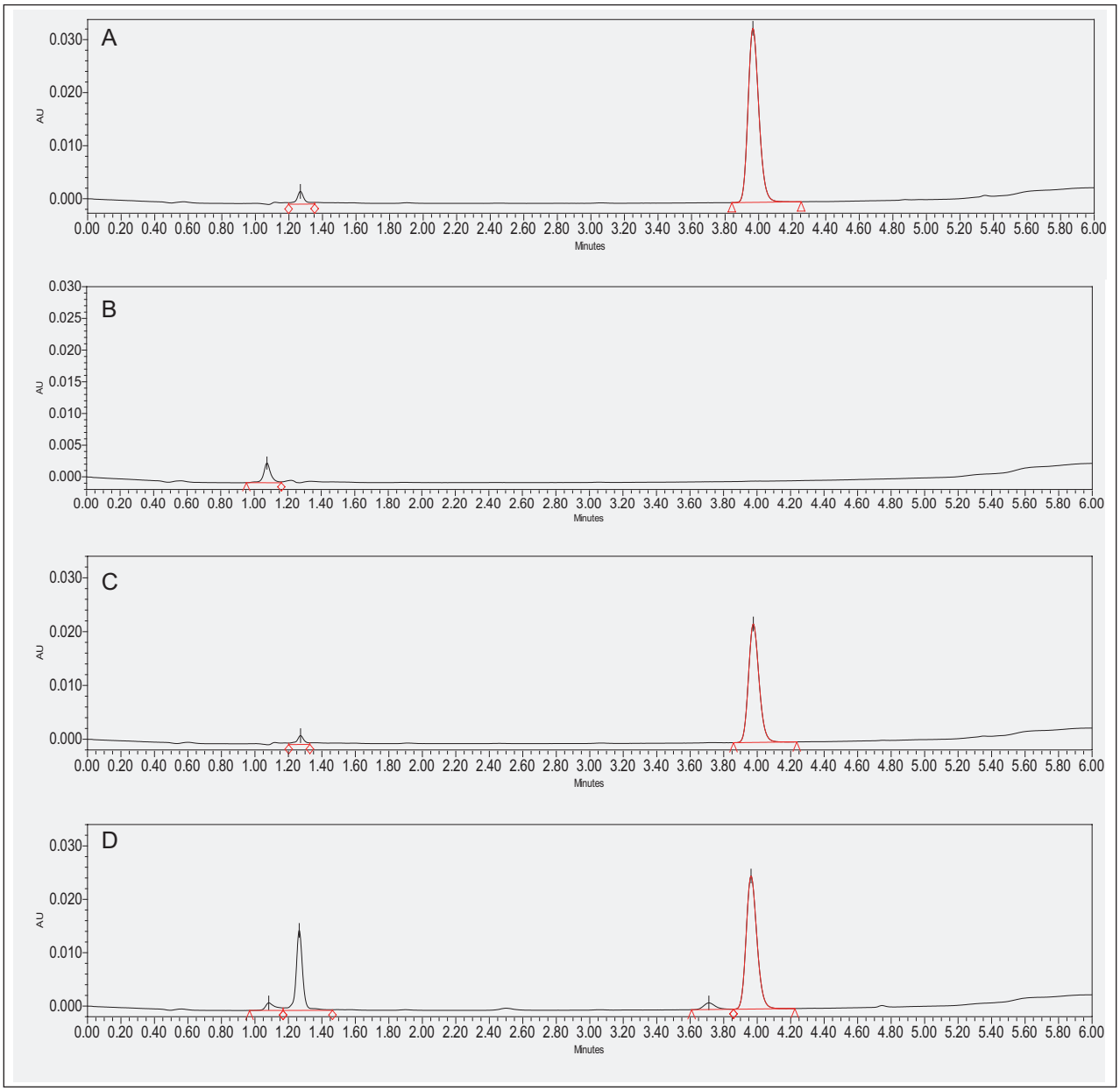
Sample preparation. Generic PG-melphalan was reconstituted to 5 mg/mL using the sterile diluent provided by the manufacturer, while lyophilized CE-melphalan was reconstituted with 0.9% sodium chloride injection. CE-melphalan IV bags were prepared at concentrations of 1 and 2 mg/mL in 0.9% sodium chloride injection, while generic PG-melphalan IV bags were prepared at concentrations of 1, 1.5, and 2 mg/mL in 0.9% sodium chloride injection. CE-melphalan test solutions were prepared in 50-mL PVC bags, and generic PG-melphalan test solutions were prepared in 25-mL PVC bags. Prepared IV bags or reconstituted glass vials were stored at RT (23°C) or 4°C. Test solutions for each drug concentration at each storage temperature were prepared in triplicate.

Chemical stability evaluation. Each test solution admixture was analyzed and evaluated immediately after preparation. This process served as the initial time point evaluation for the test solutions. The solutions were then stored at RT and under refrigeration. When experiments were in progress, the RT was measured 3 times a day using a thermometer; the mean (SD) RT was 23 (0.1) °C. The refrigeration temperature was digitally monitored by our institute's monitoring services for pharmacy refrigerators and freezers. The daily mean (SD) temperature over the days of the experiments was 3.97 (0.06) °C. The test solutions in the bags were thoroughly mixed prior to sampling. For bags of CE-melphalan stored at RT or under refrigeration, aliquots of CE-melphalan test solution were removed from each bag at 0, 2, 4, 6, 8, 12, and 24 hours. For reconstituted glass vials of CE-melphalan stored at RT or 4°C, aliquots were drawn at 24 and 48 hours. For bags of PG-melphalan at RT, aliquots were drawn at 0, 1, 2, 3, 4, and 6 hours, and for bags stored at 4°C, aliquots were drawn at 0, 2, 4, 6, 8, and 24 hours. For reconstituted glass vials

stored at RT, aliquots were drawn at 2, 3, 4, and 6 hours.

Melphalan concentrations in both test solution formulations were determined using an Agilent 1290 ultrahigh-performance liquid chromatography system (Agilent Technologies) coupled with an ultraviolet detector.[f] A 5-point standard calibration curve was created using freshly prepared stock solutions in methanol. Chromatographic separation was performed using Chromolith RP-18 endcapped column (100 x 2 mm, 1.5 µm particle size, EMD Millipore).[g] The mobile phase consisted of phase A (0.1% formic acid in water) and phase B (0.1% formic acid in methanol) and was delivered at 400 µL/min. Ultraviolet detection was performed at 260 nm. The autosampler injection volume was set at 5 µL, and under these conditions, melphalan was eluted at 4 minutes. The intraday coefficient of variation was 5.65%, while the interday coefficient of variation of 6.46%. These conditions were stability indicating, as determined by accelerated degradation of melphalan exposed to heat (95°C) and to acidic (0.1 N hydrochloric acid) and basic (0.1 N sodium hydroxide) conditions. As described in Figure 1, the degraded products of

Figure 1. Representative chromatograms of intact melphalan (panel A) and degradation products. The other panels illustrate the effects of forced degradation of melphalan by heat (95°C) (B), 0.1 N hydrochloric acid (C), and 0.1 N sodium hydroxide (D). AU indicates absorbance units.



melphalan were sufficiently separated from the parent drug.

Duplicate high performance liquid chromatography determinations were performed for each test solution at each time point. The measured drug concentration at each time point was calculated against the reference standard curve using Agilent Technologies' Mass Hunter Software.[h] The initial melphalan concentrations at time 0 were defined as 100%, and the subsequent sample concentrations were expressed as percentages of the initial concentrations. Chemical stability was defined as retention of at least 90% of the initial melphalan concentration (≤10% degradation).

Results

All admixtures were clear and colorless when viewed under normal room light and under a high-intensity light (Tyndall) beam. All CE-melphalan (1 and 2 mg/mL) and generic PG-melphalan (1, 1.5, and 2 mg/mL) admixtures and reconstituted CE-melphalan (5 mg/mL) vials stored at RT and 4°C were clear, initially and throughout the study period. Similarly, PG-melphalan (2 mg/mL) admixture and reconstituted vials (5 mg/mL) stored at RT were clear and colorless, but those stored at 4°C showed precipitation after 6 hours and within 2 hours, respectively.

The stability results for CE-melphalan, PG-melphalan, and the reconstituted vials of both drugs are shown in Tables 1, 2, and 3, respectively. Melphalan was considered stable if the percent concentration at different time points was greater than 90% of the initial concentration at time 0. Admixtures of CE-melphalan and 0.9% sodium chloride injection at a concentration of 1 mg/mL in IV bags was stable for 6 hours at RT and 8 hours at 4°C (Table 1). CE-melphalan at a concentration of 2 mg/mL in IV bags was stable for 24 hours at both RT and 4°C. CE-melphalan reconstituted in 0.9% sodium chloride to a concentration of 5 mg/mL in glass vials was stable for 48 hours at both RT and 4°C (Table 3). In comparison, generic PG-melphalan admixed with 0.9% sodium chloride at concentrations of 1, 1.5, and 2 mg/mL in IV bags was stable for only 1, 2, and 2 hours, respectively, at RT (Table 2). PG-melphalan at concentrations of 1, 1.5, and 2 mg/mL in IV bags was stable for 2, 4, and 4 hours, respectively, at 4°C. PG-melphalan solution at a concentration of 2 mg/mL formed precipitate at 4°C after 6 hours, as previously reported.[13] PG-melphalan at a concentration of 5 mg/mL in glass vials was stable for 6 hours at RT but precipitated within 2 hours at 4°C (Table 3). CE-melphalan and PG-melphalan stability curves at RT and 4°C are presented in Figures 2 and 3, respectively.

In addition, we estimated the effective doses of CE-melphalan and PG-melphalan administered to patients using the following equation:

$$ED = [100 - (a \times R) - (b \times R)],$$

where ED is the percent effective dose, a is the time elapsed (in minutes) from melphalan IV bag preparation to infusion initiation, b is the infusion length (30 or 480 minutes), and R is the rate of degradation from Table 4 (depending on melphalan formulation and concentration). We first determined R at RT for melphalan in PVC bags at various concentrations over specific time periods (Table 4) using linear regression analysis (Figure 4). The rate of degradation is inversely related to the melphalan concentration, with the highest rate of degradation occurring at the lowest melphalan concentrations in IV bags. The effective dose administered depends on (1) the type of melphalan formulation (PG-melphalan vs CE-melphalan), (2) the melphalan concentration, (3) the time from preparation of the IV bag to the start of infusion, and (4) the length of infusion (30 minutes vs 480 minutes). For example, if an infusion begins 75 minutes after bag preparation, the calculated effective dose for generic melphalan at a concentration of 1.5 mg/mL for a 30-minute infusion is 92.87%. For CE-melphalan at a concentration of 2 mg/mL, the calculated effective dose is 99.5% for a 75-minute preparation time and a 30-minute infusion time and 97.29% for a

Table 1. Stability of CE-Melphalan in 0.9% Sodium Chloride Injection in IV bags at Various Concentrations

CE-Melphalan Concentration	Percentage of Initial Concentration Remaining, Mean (SD)					
	2 h	4 h	6 h	8 h	12 h	24 h
			Room Temperature			
1 mg/mL	99.03 (1.96)	97.19 (1.77)	93.26 (0.96)	82.02 (3.17)	64.19 (3.10)	50.97 (5.95)
2 mg/mL	101.1 (2.77)	97.56 (2.0)	100.72 (2.76)	97.92 (1.07)	95.81 (1.97)	93.77 (1.80)
			Refrigeration at 4°C			
1 mg/mL	97.49 (1.00)	97 (1.41)	95.16 (1.15)	91.15 (0.33)	76.77 (3.15)	62.84 (4.44)
2 mg/mL	97.91 (2.92)	102.11 (3.82)	99.05 (5.75)	98.79 (3.95)	96.37 (2.12)	95.87 (1.01)

Abbreviation: IV, intravenous.

Table 2. Stability of PG-Melphalan Admixed With 0.9% Sodium Chloride Injection in IV bags at Various Concentrations

Generic PG-Melphalan Concentration	Percentage of Initial Concentration Remaining, Mean (SD)					
	1 h	2 h	3 h	4 h	6 h	8 h
Room Temperature						
1 mg/mL	97.93 (7.57)	86.63 (3.16)	73.73 (5.24)	63.32 (9.53)	50.06 (4.81)	ND
1.5 mg/mL	97.5 (0.51)	92.38 (1.91)	88.16 (0.6)	73.73 (5.88)	55.26 (4.55)	ND
2 mg/mL	101.34 (0.75)	94.62 (2.91)	89.24 (0.51)	86.86 (2.01)	74.66 (8.65)	ND
Refrigeration at 4°C						
1 mg/mL	ND	92.32 (1.74)	ND	87.83 (1.22)	74.68 (3.01)	55.82 (2.2)
1.5 mg/mL	ND	96.44 (3.48)	ND	91.33 (2.3)	84.51 (1.95)	79.24 (0.49)
2 mg/mL	ND	94.69 (1.43)	ND	91.2 (1.25)	82.68 (1.18)	ND[a]

Abbreviations: IV, intravenous; ND, not determined.
[a]Precipitate formed.

Table 3. Stability of CE-Melphalan and Generic PG-Melphalan in Reconstituted Glass Vials

Melphalan Formulation	Percentage of Initial Concentration Remaining, Mean (SD)					
	2 h	3 h	4 h	6 h	24 h	48 h
Room Temperature						
Generic PG-melphalan 5 mg/mL	98.26 (6.48)	94.09 (1.93)	92.59 (0.28)	90.66 (0.43)	ND	ND
CE-melphalan 5 mg/mL	ND	ND	ND	ND	99.44 (2.36)	93.9 (2.40)
Refrigeration at 4°C						
Generic PG-melphalan 5 mg/mL	ND[a]	ND[a]	ND[a]	ND[a]	ND[a]	ND[a]
CE-melphalan 5 mg/mL	ND	ND	ND	ND	99.84 (1.38)	94.6 (1.30)

Abbreviation: ND, not determined.
[a]Precipitate formed

480-minute infusion and a 75-minute preparation time.

Discussion

Melphalan is highly effective when administered as a conditioning regimen for transplantation.[1-5] Previous studies showed that a longer duration of melphalan exposure (5-6 hours) results in a 3-fold higher intracellular concentration, which might improve treatment outcomes.[14] However, the most commonly used PG-melphalan formulation has a very short period of stability (60 minutes) at a concentration of 0.45 mg/mL and is recommended to be infused over 15 minutes.[8] This makes it very difficult to prepare and infuse the drug in a timely manner. Because of its short period of stability, the drug is prepared on call, often by a satellite pharmacy located very close to the patient. Operationally, this is a huge challenge for many small hospitals and can lead to substantial wastage of the drug. In addition, because of PG-melphalan's rapid degradation, the actual dose infused may be subtherapeutic. In this study, we compared the stability of CE-melphalan and PG-melphalan at various concentrations in the usual formulation used for patient care.

With increasing drug concentrations, there is a greater likelihood of improvement in the chemical stability of the drug, but increasing concentrations can also decrease the physical stability of drugs due to the formation of precipitates.[11,12] Because PG-melphalan has a short period of stability and a tendency to precipitate under refrigeration, we tested concentrations of 1, 1.5, and 2 mg/mL to empirically find a concentration with good chemical and physical stability. We designed different sampling schemas for PG-melphalan and CE-melphalan because of the vast differences in the drugs' stability. Because PG-melphalan has a short duration of stability, we collected samples every hour (up to 4 hours) at RT and every 2 hours at 4°C.[13] Because CE-melphalan is more stable than PG-melphalan at both RT and 4°C,

Figure 2. Stability curves of (A) CE-melphalan (1 and 2 mg/mL), and (B) PG-melphalan (1, 1.5, and 2 mg/mL) admixtures in 0.9% sodium chloride solution stored at room temperature (RT) (23°C). Stability was defined as the retention of at least 90% of the initial melphalan concentration (ie, ≤10% degradation).

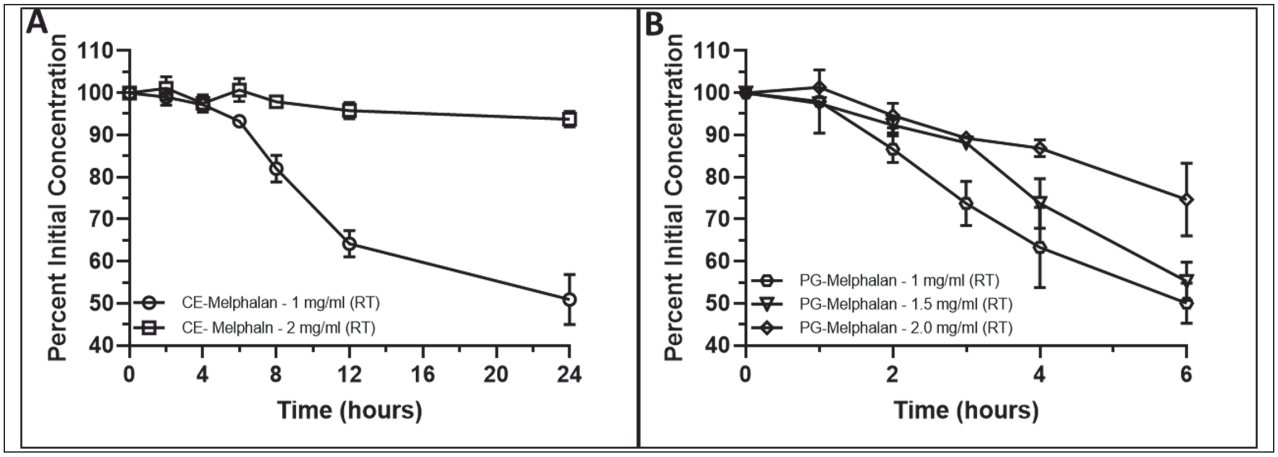
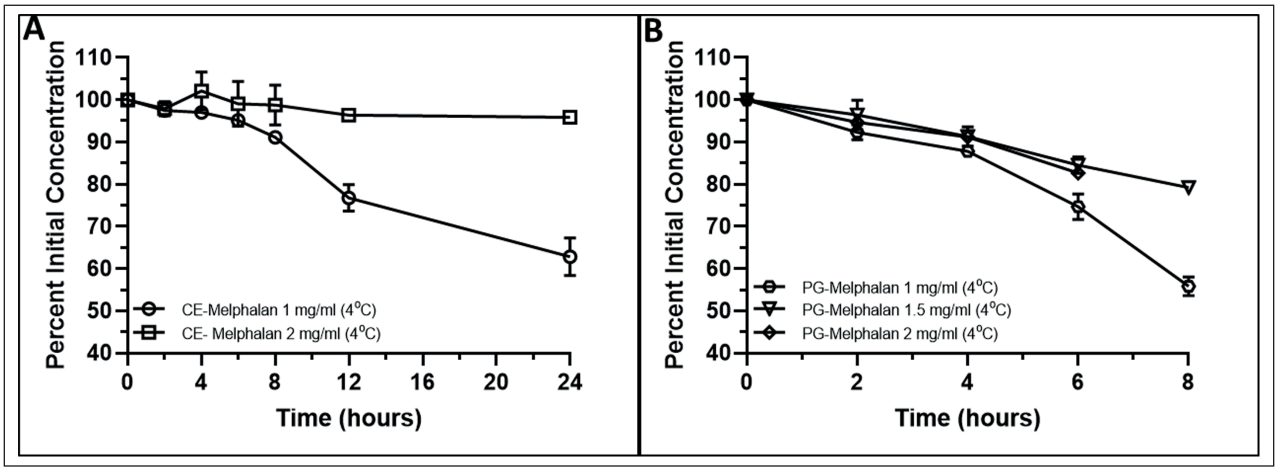


Figure 3. Stability curves of (A) CE-melphalan (1 and 2 mg/mL), and (B) PG-melphalan (1, 1.5, and 2 mg/mL) admixtures in 0.9% sodium chloride solution stored at 4°C. Stability was defined as the retention of at least 90% of the initial melphalan concentration (ie, ≤10% degradation).



samples were collected every 2 hours (up to 8 hours) and the final samples were collected after 24 hours.[10]

Observations from this study show that CE-melphalan is unequivocally more stable than PG-melphalan. The CE-melphalan admixture at a concentration of 2 mg/mL was stable for 24 hours at both RT and 4°C; at a concentration of 1 mg/mL, they were stable for 6 hours at RT and 8 hours at 4°C (Table 1). Irrespective of concentration, these admixtures were clear and colorless and did not precipitate when stored at RT or 4°C over 24 hours. Our CE-melphalan stability results for admixtures stored in IV bags are in accordance with those for these concentrations of admixtures stored in glass vials.[10] On the basis of our findings regarding the extended stability of CE-melphalan, we are investigating the effect of long (8-hour) versus standard (30-minute) durations of melphalan infusions on treatment outcomes in a clinical trial (ClinicalTrials.gov identifier, NCT03417284) in patients with multiple myeloma undergoing hematopoietic stem cell transplantation.

Interestingly, we also found that PG-melphalan admixtures at higher concentrations (1.5 and 2 mg/mL) are stable for 2 hours at RT and 4 hours at 4°C. Although these periods of stability are shorter than those of CE-melphalan, they are markedly better than the 1-hour period of stability previously reported. Thus, preparing higher concentrations of PG-melphalan admixtures could allow more time to prepare and infuse the drug. At our institution, PG-melphalan is prepared at a concentration of 1.5 mg/mL and infused over a 30-minute duration. Based on the drug's degradation rate (Table 4, Figure 4) and preparation time (including the

time to prepare the IV bag, conduct dispensing checks within the pharmacy, and deliver the IV bag to the floor, followed by priming of drug, bag check by nurses and hang the bag, and start infusion), the calculated effective dose for PG-melphalan at a concentration of 1.5 mg/mL and with a 75-minute preparation time and 30-minute infusion time was 92.87%. For CE-melphalan at a concentration of 2 mg/mL and with a 75-minute preparation time, the calculated effective doses were 99.5% for a 30-minute infusion time and 97.29% for an 8-hour infusion time. Other institutes and hospitals using different melphalan concentrations or preparation times can calculate the effective doses administered using the rates of degradation described in Table 4 and can change their workflow accordingly to improve the effective administered melphalan doses, especially for PG-melphalan. In contrast, for CE-melphalan at a concentration of 2 mg/mL, the rate of degradation is so low that the effective dose is almost 100% for 30-minute and 8-hour infusion times.

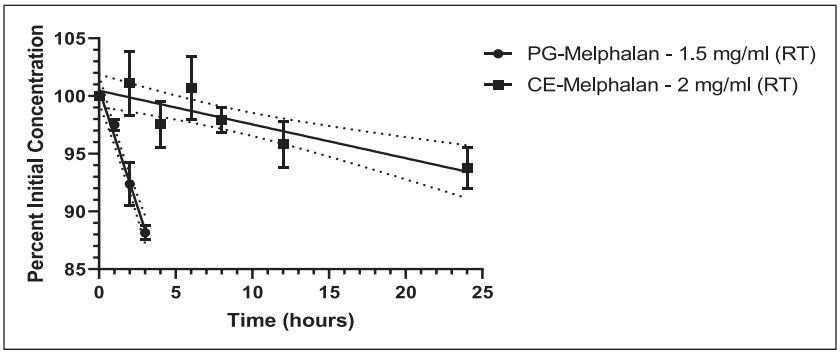
In our study, reconstituted CE-melphalan vials (5 mg/mL) were stable for 48 hours at RT and 4°C (Table 3), and the solutions were clear and without precipitation. By contrast, reconstituted PG-melphalan formed precipitate within 2 hours when stored at 4°C. The extended physical and chemical stability of reconstituted CE-melphalan suggests that any leftover drug in the vial could be used for the next dose if stored at 4°C, which may reduce drug wastage. Moreover, consideration should be given to increasing the PG-melphalan doses to account for the corresponding degradation rates and infusion times, because some medical facilities might not be able to switch to CE-melphalan due to the potentially huge difference in wholesale acquisition cost per 50-mg vial between the 2 melphalan formulations ($2,000 for CE-melphalan vs $200-$1,972 for PG-melphalan).

Table 4. Estimated Rate of Degradation of Melphalan Admixtures in PVC Bags

Melphalan Formulation at Room Temperature	Rate of Degradation, %/min	Time Period[a]
PG-melphalan 1 mg/mL	0.1502	0-3 h
PG-melphalan 1.5 mg/mL	0.0678	0-3 h
PG-melphalan 2 mg/mL	0.0650	0-3 h
CE-melphalan 1 mg/mL	0.0184	0-6 h
CE-melphalan 2 mg/mL	0.0049	0-24 h

Abbreviation: PVC, polyvinyl chloride.
[a]Rate of degradation calculated over the indicated time period.

Figure 4. Rates of degradation of PG-melphalan (1.5 mg/mL) at room temperature over a 3-hour period and CE-melphalan (2 mg/mL) at room temperature over a 24-hour period.



Conclusion

Compared to generic PG-melphalan, CE-melphalan admixed with 0.9% sodium chloride injection has a longer duration of stability in IV bags and glass vials at RT and 4°C. Our results indicate that CE-melphalan solutions prepared with 0.9% sodium chloride injection in PVC bags are physically and chemically stable for 6 hours at RT at a concentration of 1 mg/mL and for 24 hours at RT at a concentration of 2 mg/mL. CE-melphalan solutions prepared with 0.9% sodium chloride injection in glass vials at a concentration of 5 mg/mL are stable for 48 hours at RT and 4°C. These new stability data support the investigation of prolonged CE-melphalan infusion times in patients receiving hematopoietic stem cell transplantations.

[a]TLC Pharmaceutical Standards, Newmarket, ON, Canada, lot L3Y 7B6.
[b]Fisher Scientific, Fair Lawn, NJ.
[c]Spectrum Pharmaceuticals/Acrotech Biopharma, East Windsor, NJ, lot AH5372 (expiration, August 2020).
[d]Mylan, Canonsburg, PA, lot N1700790 (expiration, October 2019).
[e]Baxter Healthcare, Deerfield, IL, 50-mL bags (lot P382051; expiration, August 2019) and 25-mL bags (lot P383059; expiration, May 2019).
[f]Agilent Technologies, Santa Clara, CA.
[g]Chromolith fast gradient, RP-18e, (100 × 2 mm, 1.5 µm), EMD Millipore, Billerica, MA.
[h]Mass Hunter Software, Agilent Technologies.

Disclosures

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At the time of the study Dr. Ciurea was affiliated with Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX.

Additional information

Dr. Kawedia contributed to the study design, performed the experiments, and wrote the first draft of the manuscript; Dr. Ramchandran and Dr. Liu contributed to the development of the high-performance liquid chromatography assay and performed the experiments and analysis of the melphalan samples; and Dr. Ciurea contributed to the study design, data interpretation, and drafting of the manuscript. All authors provided interpretation of data, critically edited and revised the manuscript for important intellectual content, and approved the final version of the text.

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