Propylene glycol-free melphalan as conditioning regimen for autologous transplantation in myeloma

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Practice points

- Propylene glycol-free melphalan (PGF-Mel) is a newer formulation of melphalan that incorporates Captisol® to enhance stability while maintaining solubility.
- PGF-Mel has been investigated in two Phase II clinical trials, both showed adequate safety and tolerability data.
- PGF-Mel benefits over current propylene glycol enabled melphalan:
 - More stable, which eliminates the time constraints related to preparing the drug and infusing it. It also allows for testing different infusion schedules in trials;
 - Marginally higher bioavailability, which might translate into improved clinical benefit. This may be a consequence of a more stable product that ensures delivery of intended dose without loss during preparation time.

High-dose melphalan has been the drug of choice for preparative regimens for autologous stem cell transplantation in multiple myeloma. Propylene-free melphalan (Evomela™) is a newer formulation of melphalan, which incorporates Captisol® to produce a stable product upon reconstitution. In addition to avoiding propylene glycol with its' potential side effects, this approach improves the overall stability of reconstituted melphalan and can ensure intended dose delivery. In this paper, we review the published literature regarding this formulation. We focus on its' chemistry, pharmacokinetics and clinically available data for its use in myeloma autologous stem cell transplantation setting.

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High-dose chemotherapy and autologous stem cell transplantation (ASCT) is currently considered standard of care in symptomatic, transplant eligible multiple myeloma (MM) patients [1]. High-dose melphalan has been the chemotherapy of choice based on its single agent activity in myeloma, reliable myeloablation and also based on comparison with total body radiation approaches in randomized clinical trials [2,3]. Melphalan, a bifunctional alkylator, is marginally soluble and has limited chemical stability once reconstituted and diluted. To overcome the solubility issue, propylene glycol has been traditionally used as a solubilizer in melphalan products such as Alkeran™ for injection. Propylene glycol could potentially contribute to some side effects, especially when used in large amounts over short infusion durations. These side effects include renal dysfunction, cardiac arrhythmias, hyperosmolality, increased anion gap metabolic acidosis and sepsis-like syndrome [4–6]. These adverse side effects are not typically well defined or clearly attributed to propylene glycol during high-dose therapy

KEYWORDS

- high-dose chemotherapy
- melphalan • multiple myeloma • propylene glycol-free melphalan

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and ASCT. Propylene glycol-free melphalan (PGF-Mel) avoids the use of propylene glycol by incorporating the beta cyclodextrin (Captisol®). Beta cyclodextrin (Captisol)-stabilized products in current clinical use include intravenous medications such as voriconazole (VFEND® intravenous), amiodarone (NEXTERONE® premixed injection) and recently approved carfilzomib (Kyprolis® for injection).

The need for melphalan

High-dose melphalan is the drug of choice for high-dose therapy in MM in the setting of autologous transplantation. Approximately 6500 autologous transplants are performed annually for MM in the USA and the vast majority (>94%) of them use melphalan-based conditioning regimens (Center for International Blood and Marrow Transplant Research, Plasma Cell Disorders Working Committee).

Clinical trials with PGF-Mel

PGF-Mel has been investigated in two consecutive clinical trials. The first study, a Phase IIA clinical trial, was conducted to mainly compare the pharmacokinetics of PGF-Mel versus Alkeran in a cross-over design and secondarily to investigate the safety of this product. The Phase IIB study on the other hand investigated the efficacy of this product by itself in inducing myeloablation, subsequent recovery and remission induction

following ASCT. Following is a summary of the findings from these two trials.

• Phase IIA study

This was an open-label, randomized, cross-over design study where PGF-Mel and Alkeran were given alternatively in the same MM patients undergoing autologous transplantation [7]. The primary end point of this study was to assess whether PGF-Mel was bioequivalent to Alkeran. Additionally, the efficacy of PGF-Mel and Alkeran in achieving myeloablation and the safety and tolerability of PGF-Mel in comparison to Alkeran were assessed. In this study, transplant candidate patients with either symptomatic *de novo* or relapsed MM were included if they were 70 years of age or younger with adequate organ function.

A total of 24 patients were enrolled, all received both formulations of melphalan (Alkeran and PGF-Mel) each at a dose of 100 mg/m² each (based on actual or ideal body weight). The duration of infusion of the melphalan doses varied between 28 and 44 min with mean infusion times of 32.1 and 32.6 min for the Alkeran and PGF-Mel infusions, respectively.

The study population consisted of 13 males (54%) and 11 females (46%) and the majority of patients (79%) were Caucasian. The median (range) age was 58 (48–65) years. 62.5% of the patients had stage III disease. The mean (SD) number of years since initial diagnosis was 1.6 (1.85) years.

In terms of efficacy of myeloablation, all patients achieved myeloablation at a median of 3 days posttransplant and all successfully achieved neutrophil engraftment at a median of 11 days post-transplant. There were no differences in the median times to myeloablation or engraftment if Alkeran was given first or PGF-Mel was given first.

For toxicity, all patients in this study reported at least one treatment-emerging adverse event (TEAE). Individual TEAEs that were reported in ≥50% of patients were nausea, diarrhea, vomiting, hypokalemia, fatigue, thrombocytopenia, decreased appetite and dizziness. The most frequently reported TEAEs during days -3 and 0 of transplant were fatigue, nausea and hypokalemia. The impact of individual chemotherapy drugs or propylene glycol on these adverse events is clearly difficult to be determined. However, the order in which chemotherapy was given could have contributed to different side effects. For example, during the study period, the following adverse events occurred more

Table 1. Summary of nonhematologic toxicities experienced by more than 25% of the patients.

Adverse event	Patients, n (%)
Diarrhea	57 (93)
Nausea	55 (90)
Fatigue	47 (77)
Hypokalemia	45 (74)
Vomiting	39 (64)
Hypophosphatemia	30 (49)
Decreased appetite	30 (49)
Pyrexia	29 (48)
Constipation	29 (48)
Mucosal inflammation	23 (38)
Dizziness	23 (38)
Peripheral edema	20 (33)
Stomatitis	17 (28)
Abdominal pain	17 (28)
Dysgeusia	17 (28)
Dyspepsia	16 (26)

Figure 1. Propylene glycol-free melphalan. Propylene glycol-free melphalan incorporates captisol into melphalan. Captisol has a hydrophobic interior, once it associates with melphalan, the complex has a hydrophilic exterior.

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frequently (≥ 2 patient difference) when Alkeran was given first (nausea [eight vs six patients], fluid retention [five vs three patients], edema [four vs two patients], headache and constipation [three vs one patient], and taste changes, rash and left bundle branch block [two vs zero patient]), while the following adverse events occurred more frequently (≥ 2 patients difference) when PGF-Mel was given first (dizziness [four vs one patient]). Grade 3–4 TEAEs were reported in 17 (71%) patients. The most frequently reported grade 3 TEAEs were fatigue, nausea, diarrhea, mucositis, hypokalemia, anemia and febrile neutropenia. The only grade 4 TEAEs reported were sepsis, thrombocytopenia, leukopenia, and lymphopenia, neutropenia and hypophosphatemia. Most of these grade 3–4 TEAEs were hematological and considered related to treatment.

• Phase IIB study

In this Phase IIB study, PGF-Mel (200 mg/m^2) was administered as two consecutive daily doses

of 100 mg/m^2 each in an open-label, multicenter study with two main goals: to confirm its safety and to confirm efficacy as a high-dose conditioning regimen for patients with MM undergoing ASCT [8].

A total of 61 patients (26 females, 43%) with a median age of 62 years (range: 32–73) were enrolled. 80% of the patients were white, 18% were African-Americans and most (59%) had an Eastern Cooperative Oncology Group performance status of 0. 48% had standard-risk cytogenetics, 15% had high-risk cytogenetics and the rest did not have cytogenetic information available. Most patients (92%) received upfront ASCT, while 8% had relapsed disease following a prior ASCT. Most patients (87%) had one prior therapy prior to ASCT.

In terms of efficacy as a myeloablative regimen, all patients achieved myeloablation at a median time of 5 days post-ASCT, and all successfully achieved neutrophil and platelet engraftment with median times of 12 and 13 days post-ASCT, respectively. Treatment-related mortality

Figure 2. Propylene glycol melphalan after injection into blood. Propylene glycol melphalan dissociates into melphalan and captisol following injection into blood.

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on day 100 was 0%. Myeloma response at day 100 was calculated using uniform response criteria developed by the International Myeloma Working Group (IMWG) criteria [9] and the overall response rate (according to independent, blinded review) was 100% with an overall complete response rate of 21% (13% stringent complete response; 8% complete response) and overall partial response rate of 79% (61% very good partial response; 18% partial response).

In terms of toxicity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), all patients (100%) had at least one grade 4 hematologic TEAE indicative of myeloablation. In terms of nonhematologic TEAE, 100% had at least one nonhematologic TEAE. grade 3 nonhematologic TEAEs were reported in 69% of patients and grade 4 in only 10% of patients (Table 1). Grade 3 nonhematologic TEAEs reported in $\geq 5\%$ of patients were hypophosphatemia, hypokalemia, mucosal inflammation, hyperglycemia, stomatitis, hypocalcemia and hypertension. Grade 4 nonhematologic TEAEs included hypophosphatemia (four patients), sepsis (two patients), hematochezia (one patient) and hypokalemia (one patient).

Mucositis and stomatitis were carefully assessed since gastrointestinal toxicity remains the dose-limiting toxicity of melphalan. The incidence of grade 3 mucositis and stomatitis was 10 and 5%, respectively, with no NCI CTCAE grade 4 mucositis or stomatitis reported. In this study, 75% of patients had a shift in mucositis score from the WHO grade 0 at baseline to a higher grade on study, out of which 13% of patients reported the WHO grade 3 as the worst post-treatment mucositis over the course of the study. For the rest of the patients, the worse mucositis that they had experienced was either grade 0 (22%), grade 1 (35%) or grade 2 (32%).

These two studies confirmed the efficacy and acceptable safety profile of the new PGF-Mel formulation, as a high-dose conditioning regimen for autologous in patient with MM.

Safety & tolerability

The above-mentioned studies demonstrate that the new PGF-Mel formulation is safe with good tolerance in both Phase IIA and IIB settings. The toxicity profile is overall similar to that of melphalan with a signal for lower incidence of mucosal toxicity that needs to be explored in larger studies. Reassuringly, there were no treatment-related mortality events across both studies.

Propylene glycol-free melphalan

• Chemistry

PGF-Mel incorporates Captisol brand of β -cyclodextrin sulfobutyl ethers and sodium salts ($[\text{SBE}]_{7\text{m}}\text{-}\beta\text{-CD}$) (Figure 1). Captisol has a hydrophobic interior and, once associated with melphalan, the complex has a hydrophilic exterior. Once transfused intravenously, the melphalan dissociates from Captisol, leaving melphalan free to exert its activity (Figure 2).

• Pharmacokinetics & metabolism of PGF-Mel

Animal studies suggested that the presence of β -cyclodextrin ($[\text{SBE}]_{7\text{m}}\text{-}\beta\text{-CD}$, Captisol in the intravenous delivery vehicle did not have any significant effects on whole blood or plasma disposition or renal excretion of melphalan in rats [10]. In the clinical setting, PGF-Mel pharmacokinetic studies were tested in a cross-over design in the above-mentioned Phase IIA clinical trial. In this study, pharmacokinetic levels were drawn just prior to chemotherapy infusion and at ten postdose time points up to 8 h after the end of the PGF-Mel and Alkeran infusions. Plasma levels of melphalan were determined by a sensitive LC-MS/MS method. The pharmacokinetic measures were determined using WinNonlin 6.2 and analysis of the log-transformed systemic exposure parameters (i.e., C_{max} and AUC measures) was used to evaluate bioequivalence. Based on the noncompartmental analysis, the geometric mean ratios for the model-estimated C_{max} , $\text{AUC}_{0-\infty}$ and AUC_{0-t} were 112.00, 110.90 and 110.77%, respectively, and the associated 90% CIs were contained within 80.00–125.00%, demonstrating bioequivalence based on these parameters. A compartmental analysis was also undertaken to confirm the results of the statistical comparisons based on the parameters estimated by noncompartmental analysis. The plasma melphalan concentration–time data after intravenous administration of both formulations was well described by a two-compartment intravenous infusion model. As expected, the mean values for C_{max} and $\text{AUC}_{0-\infty}$ were higher (~35 and ~20%, respectively) for the compartmental compared with the noncompartmental analysis. While there were small numerical differences in the geometric

mean ratios and associated 90% CIs, the latter were contained within 80.00–125.00% for both analyses. The compartmental analysis, therefore, confirmed the conclusions of bioequivalence from the noncompartmental analysis. Additionally, PGF-Mel resulted in marginally, but statistically significant, higher systemic drug levels than Alkeran (~110%; $p < 0.05$).

The PGF-Mel formulation results in a stable drug [10] that will deliver the exact intended dose, while melphalan in its' current formulation degrades quickly which could potentially result in delivery of suboptimal doses. Therefore, current melphalan ASCT protocols make sure that melphalan is infused within an hour of reconstitution which implicates the need to have tight control on the process from the moment of reconstitution to infusion. On the other hand, having this formulation eliminates the need to have these time constraints, which is practically important, especially in busy transplant units.

Conclusion

PGF-Mel formulation is safe and well tolerated in MM preparative regimens and provides an alternative to Alkeran. Because of the stability of the product, future studies should focus on incorporating this formulation into other preparative regimens such as BEAM for lymphoma, fludarabine-based combinations for allogeneic transplants and with busulfan for lymphoma or myeloma. Studies investigating other dosing schedules and fractionated dosing or escalated dosing are also needed to improve conditioning therapy for MM.

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• of interest; •• of considerable interest

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