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Disciplines

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Comments

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119

EFFECT OF BODY COMPOSITION AND RENAL FUNCTION ON THE PHARMACOKINETICS OF HIGH-DOSE MELPHALAN FOR MULTIPLE MYELOMA

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Background: High dose melphalan is the most common regimen for autologous stem cell transplantation (ASCT) for multiple myeloma (MM), but toxicity and efficacy are variable. We hypothesized that variation in body size, body composition, and renal function would explain differences in melphalan pharmacokinetics and therefore in outcomes after transplant.

Methods: We evaluated 41 patients who received melphalan 200 mg/m² on day -2 (one patient with poor renal function received 180 mg/m²). We calculated melphalan doses using ideal body weight (IBW), using adjusted IBW (ABW) for patients weighing >120% of IBW. We measured body composition using dual x-ray absorptiometry (DEXA), renal function with both iohexol clearance (Cl_{iohexol}) and the Cockcroft-Gault formula (CrCl_{CG}), and plasma melphalan concentrations using HPLC/tandem mass spectrometry. We used non-compartmental analysis to estimate melphalan clearance (Cl_{MEL}) and area under the curve (AUC_{MEL}) and linear regression modeling to identify factors associated with melphalan pharmacokinetics.

Results: Patients' mean BSA using actual weight was 1.93 m² (range 1.44-2.48). By DEXA scan, the mean lean body weight was 53.3 kg (SD 11.0) and mean fat percentage 31% (SD 9.5%). Mean iohexol clearance was 109 mL/min (range 28-163). AUC_{MEL} varied significantly, with a range of 7.6-26.6 mg*^h/L (mean 13.6, SD 3.8); Cl_{MEL} was similarly variable (mean 27.9 mL/min, SD 8.1). In univariate analyses, Cl_{MEL} was inversely related to age and directly related to weight, BSA, lean body weight, bone mineral content, Cl_{iohexol}, CrCl_{CG}, and MEL dose. Cl_{MEL} was not associated with body fat percentage, body fat weight, or body lean percentage, or with other measurements, such as hemoglobin, albumin, immunoglobulins, or M-spike. The strongest correlation with Cl_{MEL} was for CrCl_{CG}, and multivariable models showed no improved prediction of Cl_{MEL} with the addition of other factors to CrCl_{CG}. The best model for predicting AUC_{MEL} was dose/CrCl_{CG} (see table). These models consistently under-predicted AUC_{MEL} (mean prediction error -3.3% to -2.6%).

Table. Performance of linear models predicting AUC_{MEL}

Model	R ²	p-value
dose/CrCl _{CG}	0.26	0.001
dose/Cl _{iohexol}	0.11	0.04
dose/weight	0.10	0.04
dose/lean weight	0.08	0.08
dose/BSA _{IBW}	0.06	0.11
dose/BSA _{ABW}	0.04	0.23

Conclusion: A composite calculation incorporating age, weight, and serum creatinine, like CrCl_{CG}, may be the best way to choose melphalan doses but only explains 26% of drug exposure variability. Other measures of body composition were poor predictors of exposure. Further research is needed to better address the remaining variability in drug clearance and exposure.

120

COMPARATIVE COST UTILITY ANALYSIS OF PLERIXAFOR PLUS GCSF VERSUS CYCLOPHOSPHAMIDE PLUS GCSF AS SALVAGE MOBILIZATION REGIMENS IN MULTIPLE MYELOMA PATIENTS

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Introduction: Plerixafor is a novel agent that enhances the mobilization of peripheral blood stem cells (PBSCs) in lymphoma and mul-

iple myeloma (MM) patients whose cells mobilize poorly. Due to the substantial cost associated with its use, a cost utility analysis was performed to evaluate the economics of salvage Plerixafor in MM patients who failed previous mobilization.

Methods: A decision model was developed to analyze the cost utility for two salvage regimens: Plerixafor + GCSF (PG) versus Cyclophosphamide + GCSF (CG). The model assumes that patients undergo mobilization with one of the regimens, followed by apheresis and subsequent autologous transplant if CD34+ cell count is $\geq 2 \times 10^6$ cells/kg, or Bortezomib plus Dexamethasone if insufficient CD34+ cells are collected. Patients included in the model will eventually progress and die from their disease. A structured literature review was performed to collect data on the successful mobilization rate, life year gained and quality of life associated with the modeled options. The analysis was from the perspective of Jordanian Ministry of Health; the costs were based on its list prices and included the costs of medications, apheresis, autologous transplant and adverse effects management. The willingness to pay threshold was \$30,000 per quality adjusted life year (QALY). Incremental cost effectiveness ratio (ICER) was calculated by dividing the incremental average cost by the incremental QALY gained. One-way sensitivity analysis was performed to explore the impact of the uncertainty in efficacy data on the results.

Results: The model showed that PG was associated with higher probability of achieving successful re-mobilization and subsequent transplant. The average total costs associated with CG and PG were \$41,500 and \$58,400 respectively. The estimated ICER was \$52,813/QALY. (Table 1) The sensitivity analysis revealed that the ICERs ranged from \$86,500 to \$40,488 per QALY gained when the probability of PG success ranged from 60% to 95%.

Conclusion: This analysis showed that the use of Plerixafor plus GCSF as salvage mobilization regimen in MM patients was not cost effective compared to Cyclophosphamide plus GCSF from the perspective of our health care system. To our knowledge, this is the first study to describe a cost utility analysis of Plerixafor use in this indication.

Table 1. Analysis of Plerixafor plus GCSF (PG) versus Cyclophosphamide plus GCSF (CG)

Regimen	PG	CG	Incremental results
Probability of successful mobilization	0.80	0.27	0.53
Average total costs	\$58,400	\$41,500	\$16,900
Life year gained	4.3	3.8	0.50
QALY	2.58	2.26	0.32
ICER (\$/QALY gained) for PG			\$52,813

121

OUTCOME OF PATIENTS WITH NONSECRETORY MULTIPLE MYELOMA AFTER AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: More than 95% of patients with multiple myeloma have a detectable monoclonal protein either in the serum or urine. Less than 5% of patients have non-secretory myeloma (NSM), characterized by the absence of a monoclonal protein. There are limited available data on the outcome of patients with NSM (Ref. Kumar S et al.). We studied the outcomes of patients with NSM after high-dose chemotherapy and autologous hematopoietic stem cell transplantation (auto-HCT), and compared them to a matched group of patients with secretory myeloma (SM).

Methods: Between 1988 and December 2010, 1567 patients with MM received auto-HCT at our institution. We identified 31 patients with NSM and compared their outcome to a matched group of 94 patients with SM. Patients were matched for age at auto-HCT, Durie-Salmon stage, response to therapy prior to auto-HCT, and the year of auto-HCT. Variables for the two groups were compared using the conditional logistic regression method to adjust the