Cost Savings with Treosulfan and Fludarabine (Flu/Treo) Conditioning Regimen vs. RIC (Flu/Bu2 and Flu/Mel) and MAC Regimens (Flu/Bu4 and Bu4/Cy) in Patients Undergoing Allogeneic HSCT for AML or MDS

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Objective

To compare cost savings from avoided complications with treosulfan + fludarabine (Flu/Treo) conditioning regimen vs. commonly used reduced-intensity conditioning (RIC) and myeloablative conditioning (MAC) regimens in patients undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT) for acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS).

Methods

Efficacy outcomes and key complications: acute and chronic graft vs. host disease (aGVHD and cGVHD), relapse, graft failure, and veno-occlusive disease (VOD)] were compared. Phase III data used for gathering outcomes for Flu/Treo[1,2]. Published literature[3,4] used for RIC regimens (Table 1) busulfan + fludarabine (Flu/Bu2) and fludarabine + melphalan (Flu/Mel) with or without antithymocyte globulin (ATG) and MAC regimens (Table 2) busulfan + fludarabine (Flu/Bu4+/-ATG) and busulfan + cyclophosphamide (Bu4/Cy).

Table 1: Efficacy outcomes and key complications Flu/Treo vs RIC regimens

Rate of key survival outcomes	Flu/Treo[1,2]	Flu/Bu2[3,4]	Flu/Bu2 + ATG[3,4]	Flu/Mel[3,4]	Flu/Mel + ATG[3,4]
Event Free Survival (EFS) (%)	65.7%	44.0%	40.0%	56.0%	43.0%
Overall Survival (OS) (%)	72.7%	49.0%	46.0%	54.0%	50.0%
Non-Relapse Mortality (NRM) (%)	12.0%	14.0%	13.0%	25.0%	26.0%
Rate of key complications	**Flu/Treo[1,2]**	**Flu/Bu2[3,4]**	**Flu/Bu2 + ATG[3,4]**	**Flu/Mel[3,4]**	**Flu/Mel + ATG[3,4]**
Acute GvHD (Grades 3-4 at 100 days)	6.4%	2.0%	2.0%	5.0%	9.0%
Extensive Chronic GvHD (2 yrs)	19.8%	29.6%	25.1%	31.9%	17.7%
Relapse (2 yrs)	22.0%	43.0%	50.0%	19.0%	24.0%
Graft Failure (2 yrs)	0.4%	2.0%	7.0%	5.0%	11.0%
VOD (CTCAE Grade 3-4, 100 days)	0.0%	2.7%	2.7%	2.7%	2.7%

Table 2: Efficacy outcomes and key complications Flu/Treo vs MAC regimens

Rate of key survival outcomes	Flu/Treo[1,2]	Bu4/Cy[3,4]	Flu/Bu4[3,4]	Flu/Bu4 + ATG[3,4]
Event Free Survival (EFS) (%)	65.7%	48.0%	48.0%	48.0%
Overall Survival (OS) (%)	72.7%	60.0%	54.0%	53.0%
Non-Relapse Mortality (NRM) (%)	12.0%	22.0%	23.0%	24.0%
Rate of key complications	**Flu/Treo[1,2]**	**Bu4/Cy[3,4]**	**Flu/Bu2 + ATG[3,4]**	**Flu/Mel[3,4]**
Acute GvHD (Grades 3-4 at 100 days)	6.4%	9.0%	5.0%	5.0%
Extensive Chronic GvHD (2 yrs)	19.8%	35.3%	34.2%	23.9%
Relapse (2 yrs)	22.0%	29.0%	30.0%	37.0%
Graft Failure (2 yrs)	0.4%	1.0%	2.0%	4.0%
VOD (CTCAE Grade 3-4, 100 days)	0.0%	3.6%	3.6%	3.6%

Cost of key complications except graft failure retrieved from peer reviewed literature and inflation adjusted to 2024 (Table 3). Graft failure costs estimated using EncoderPro "adjusted total" payment rates for allo-HSCT (DRG 014) for 30 hospitals (excluding PPS exempt hospitals) based on total number of allogeneic transplants as reported by National Marrow Donor Program. Patients with graft failure often receive second HSCT therefore DRG payment for allo-HSCT used to calculate costs assuming ~38.5% patients undergo second allo-HSCT following graft failure[5].

Table 3: Cost of complications

Severe VOD[6]	aGvHD[7,8]	cGvHD[9,10]	Relapse[11]	Graft failure[12]
$172,323	$108,222	$379,874	$547,354	$144,802

Costs associated with complications of allo-HSCT calculated by multiplying costs/payment rates by the rate of complications associated with each regimen from a health system perspective (Figure 1).

Figure 1: Calculation of cost savings to the healthcare system

Costs savings to the healthcare system = **Reduction in rates of complications** X **Cost/payment rate for complications**

- Reduction in rates of complications
  - Complications post allo-HSCT include: VOD, aGvHD, cGvHD, relapse and graft failure so we are consistent with the table
  - Rates obtained from treosulfan pivotal trial and published literature
- Cost/payment rate for complications
  - Cost of complications, except graft failure, retrieved from peer reviewed literature and inflation adjusted to 2024 USD
  - Graft failure costs estimated using EncoderPro for DRG 014 (allogeneic bone marrow transplant)

Results

- Clinical outcomes were more favourable and rates of key complications were usually lower with Flu/Treo vs. commonly used RIC and MAC regimens
- Estimating cost implications of fewer complications with Flu/Treo suggests a reduction in costs ranging from
  - $1.8M to $17.5M over 2 years for every 100 patients treated with Flu/Treo vs. RIC regimens (Figure 2)
  - $10.3M to $10.8M over 2 years every 100 patients treated with Flu/Treo vs. MAC regimens (Figure 3)

Figure 2: Cost of complications- Flu/Treo vs RIC regimens

Flu/Treo vs. Flu/Bu2	~$15.1M ($11.2M to $19.0M) cost savings
Flu/Treo vs. Flu/Bu2 + ATG	~$17.5M ($12.2M to $22.8M) cost savings
Flu/Treo vs. Flu/Mel	~$3.5M ($3.1M to $3.9M) cost savings
Flu/Treo vs. Flu/Mel + ATG	~$1.8M ($1.2M to $2.5M) cost savings

Figure 3: Cost of complications- Flu/Treo vs MAC regimens

Flu/Treo vs. Flu/Bu4	~$10.3M ($8.8M to $11.9M) cost savings
Flu/Treo vs. Flu/Bu4 + ATG	~$10.4M (7.5M to $13.3M) cost savings
Flu/Treo vs. Bu4/Cy	~$10.8M ($9.4M to $12.2M) cost savings

Conclusion

- As treatment evolves to leverage reduced toxicity conditioning (RTC) regimens, Flu/Treo offers clinical benefit and results in a substantial reduction in total cost of care from avoided complications vs. RIC and MAC regimens
- This is likely a conservative estimate of the value of Flu/Treo given this analysis does not include QALY gains from improved OS and EFS

Limitations

- Outcomes data used for Flu/Treo was based on pivotal registration trial while data for other RIC and MAC regimens was from published literature with indirect comparisons, historical controls and spanning disparate study periods
- Costs could vary; for example, cGvHD costs could be an underestimate if recently launched novel therapies are considered
- Furthermore, in many facilities case rates are applied which could be substantially different from the payment rates DRG 014 used to estimate the cost of graft failure in this analysis

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Poster presented at ISPOR 2025, Montreal, CA: 13 May – 16 May 2025

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