Donor Lymphocyte infusion (DLI) in Myelofibrosis

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- Allogeneic hematopoietic cell transplantation (allo-HCT) remains the sole curative option for myelofibrosis (MF) achieving an estimated 3-year overall survival (OS) of roughly 50% to 60% in younger
- Relapse remains a significant problem (in up to 20% to 30% of cases)
- DLI is a potentially effective strategy for ***relapse prevention*** and management, but the optimal timing based on measurable residual disease/ chimerism analyses and the choice of regimen remain undetermine

Type of donor:

- sibling donor or unrelated donor (URD) , Haploidentical donors , with a move away from umbilical cord blood

conditioning regimen:

1. transplantation center experience
2. patient characteristics (age and performance status/comorbidities)
3. disease-specific features, as captured in such scoring systems as the Dynamic International Prognostic Scoring System (DIPSS) and Mutation-Enhanced International Prognostic Scoring System 70+ v2.0 (MIPSS70+ v2.0)

Relapse after allo-HCT:

- no prognostic score accurately predicts the risk of relapse.
- 20% to 30% of patients will relapse within 3 years, most commonly within the first 12 months

Post allo-HCT strategies to reduce the risk of overt relapse include :

- close monitoring of measurable residual disease (MRD) when a suitable mutation is present
- chimerism monitoring to guide immunosuppression weaning
- use of preemptive **adoptive immunotherapy with donor lymphocyte infusion (DLI)** if feasible and necessary

- marked variation in MRD and chimerism monitoring practices

  → DLI

- frank relaps → therapeutic approaches vary widely:
  1. from palliation and DLI
  2. reintroduction of JAK inhibitors
  3. even a second allo-HCT in selected individuals.

DLI in relapse of MF :

- the optimal timing and dosing remain undetermined in MF allo-HCT patients
- DLI can be considered “**preemptive**” when use is triggered by mixed donor chimerism or reemergence of MRD in the absence of clear relapse and “**therapeutic**” when there is evidence of clinician-defined relapse.

- DLI is most commonly delivered in an **escalating dose regimen** (EDR) or as "**bulk salvage**" therapy,
- the selection of which is determined by:
    1. disease relapse kinetics
    2. type of donor
    3. degree of T cell depletion
    4. physician choice
    5. desired clinical endpoint

efficacy of DLI following MF allo-HCT :

- only a small number of studies
- A previous single-center case series (n = 17) highlighted that preemptive DLI as an EDR for molecular relapse post-allo-HCT for MF (as evidenced by an ***increased JAK2 V617F allele burden*** determined by a highly sensitive quantitative PCR) led to molecular complete response (CR) in 8 of 8 patients, compared with 4 of 9 patients with clinical relapse achieving CR who received DLI as salvage treatment

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Donor Lymphocyte Infusion and Molecular Monitoring for Relapsed Myelofibrosis After Hematopoietic Cell Transplantation

Nico Gagelmann [1], Christine Wolschke [1], Anita Badbaran [1], Dietlinde Janson [1], Carolina Berger [1], Evgeny Klyuchnikov [1], Francis Ayuk [1], Boris Fehse [1], Nicolaus Kröger [1]

Affiliations + expand

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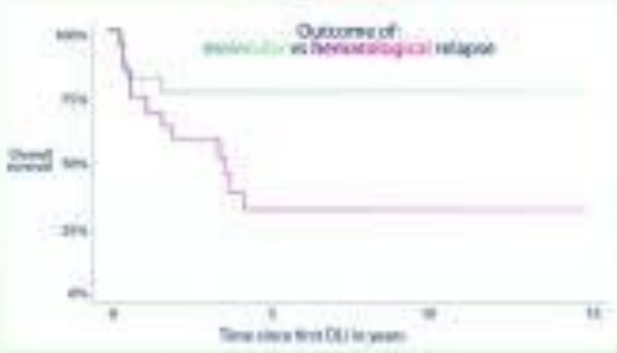
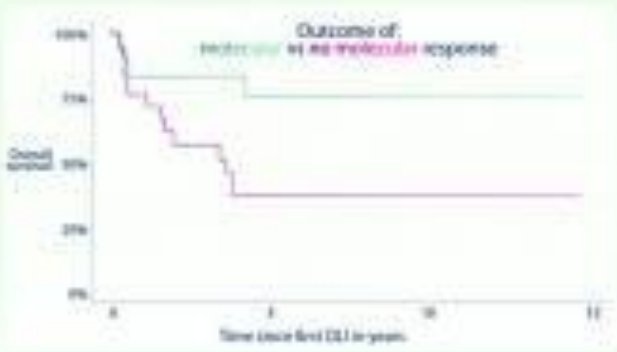
Allogenic HCT for patient with myelofibrosis

Relapse

Molecular (n=17)	Hematological (n=20)
1st DLI	1st DLI
2nd DLI (n=10)	2nd DLI (n=14)
3rd DLI (n=8)	3rd DLI (n=7)
4th DLI (n=6)	4th DLI (n=2)
5th DLI (n=5)	
Last status: Persistence, n=5 mCR, n=8 Dead, n=4 **2nd HCT, n=0**	Last status: Persistence, n=0 mCR, n=5 Dead, n=9 2nd HCT, n=6





Molecular monitoring together with DLI

Allows **early** identification of relapse

Enables **accurate** discrimination of molecular and hematological relapse

Induces **deep** responses early after 1st and 2nd infusion **without** significant risk of GvHD

Showed molecular response in half of patients **without** the development of GvHD

May **avoid** intensive salvage transplant

And overall shows **excellent** long-term outcomes

Should be **standard of care** for relapse myelofibrosis after HCT

HemaSphere

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Outcome	Total (n = 37)	Relapse		*P* Value
		Molecular (n = 17)	Hematological (n = 20)	
Overall mCR, n (%)	27 (73)	15 (88)	12 (60)	0.05
Cumulative number of DLIs to achieve mCR, median (range)	2 (1–5)	2 (1–5)	3 (1–4)	0.41
Cumulative median T-cell dose to achieve mCR $\times 10^6$ (CD3+/kg)	3.5 (0.5–101)	3 (0.5–61)	5 (0.5–101)	0.53
Patients with 2nd HCT, n (%)	6 (16)	0 (0)	6 (30)	0.004
Overall acute GvHD II–IV, n (%)	8 (22)	3 (18)	5 (25)	0.59
Overall acute GvHD grade III/IV, n (%)	4 (11)	2 (12)	2 (10)	0.49
Overall chronic GvHD, n (%)	8 (22)	6 (35)	2 (10)	0.06
mCR without GvHD, n (%)	14 (38)	7 (52)	7 (58	0.70
EFS at 5 y, % (95 CI)	40 (23–57)	59 (36–82)	25 (4–46)	0.11
OS at 5 y, % (95 CI)	53 (36–70)	77 (57–97)	32 (10–54)	0.03

EFS = event-free survival; GvHD = graft-versus-host disease; mCR = molecular complete response; OS = overall survival; TRM = treatment-related mortality.

Table 3

Events and Severity of Graft-versus-host Disease After DLI

DLI	Acute GvHD	Chronic GvHD
1st	2 (grade III: liver; grade IV: skin, liver, GI)	1 (moderate: skin, eyes)
2nd	4 (2 grade II: skin; 2 grade III: skin)	3 (1 mild: skin; 2 moderate: skin, mouth eyes)
3rd	0	1 (mild: skin)
4th	1 (grade II: skin)	4 (mild: skin)
5th	1 (grade II: liver)	0
Total	8	8

DLI = donor lymphocyte infusion; GI = gastrointestinal; GvHD = graft-versus-host disease.

DISCUSSION:

1. **molecular monitoring** enables to differentiate between molecular relapse after HCT, which is associated with significantly improved outcome in comparison with hematological relapse after HCT
2. this approach can identify and treat relapsed patients early after HCT
3. all patients who experienced subsequent relapse after having achieved mCR after first DLI could be salvaged with subsequent DLI, exhibiting long-term survival.
4. half of the patients achieve mCR without developing GvHD
5. no patient that was initially treated for molecular relapse was in need of a second HCT as salvage strategy

Conclusion:

- DLI for relapsed myelofibrosis after HCT showed excellent survival, particularly for patients with molecular relapse and who showed mCR at any time.
- Molecular CR can be achieved in half of the patients without development of debilitating GvHD