

Stato dell'arte: dose e timing delle DLI nelle terapie post-trapianto allogenico

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Corso di Formazione **GITMO**
**Trapianto e
terapie cellulari:
cellule, donatori e
condizionamenti**

Udine, 8-9 Ottobre 2026
Aula Polifunzionale Ospedale di Udine

Disclosures

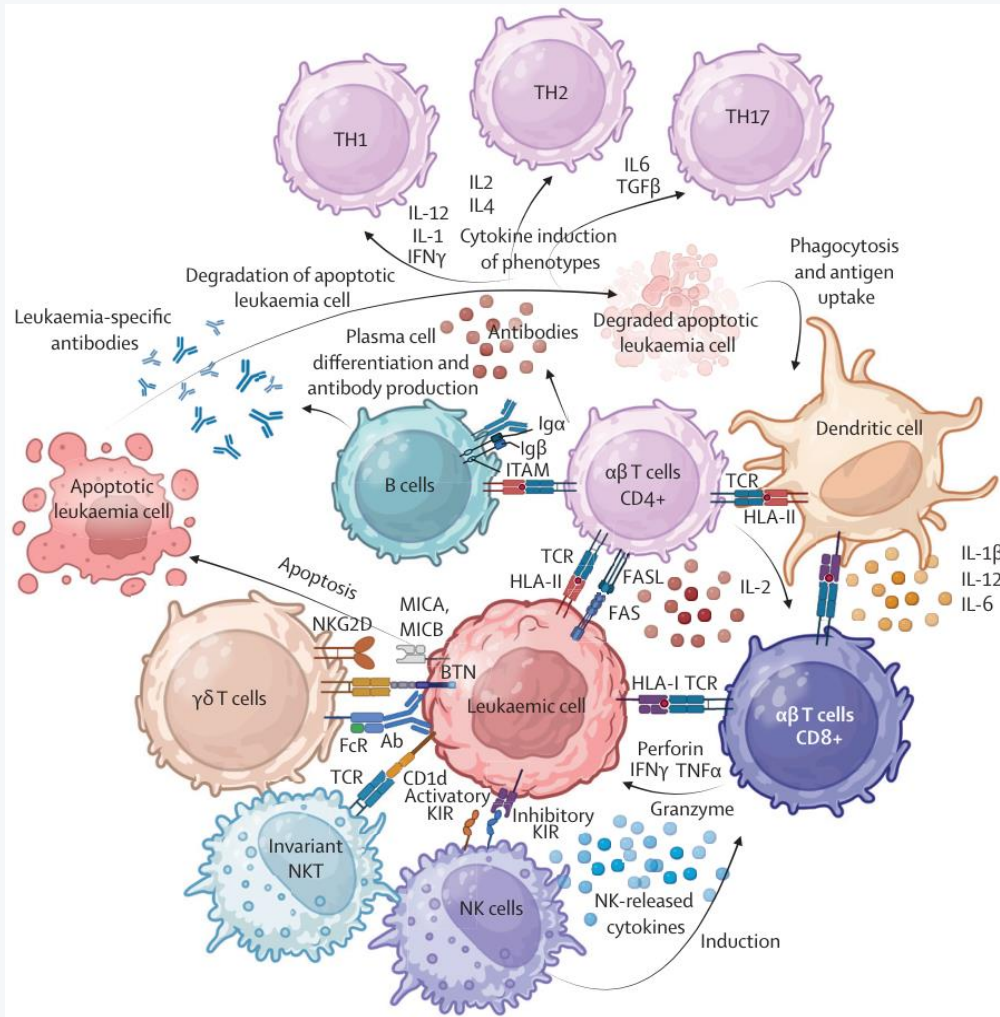
Consultant for

- Alexion
- Medac
- Pierre Fabre
- Kite Gilead
- Sanofi
- Johnson and Johnson

DLI State of art

- DLI is the reinfusion of peripheral blood lymphocytes from the original donor into the HSCT recipient.
- DLI is an immunomodulatory strategy to improve graft-versus-malignancy effect and immune surveillance
- The first DLI for treatment of relapsed disease was reported in 1990 by Kolb et al. in 3 patients with relapsed chronic myelogenous leukemia, resulting in complete hematologic and molecular remissions for all patients. 2 pts developed GVHD.

DLI Composition and GVL activity



- T cells (80–90% of the entire product), B cells (~5%), and natural killer (NK) cells (5–20%).
- Among T cells, the $\alpha\beta$ T-cell effector subset is the most represented, accounting for 90% followed by $\gamma\delta$ T cells (5–10%), $\alpha\beta$ T regulatory cells (5%) and natural killer T cells (NKT cells; <1%).
- GVHD risk

DLI are not effective if the relapse post HSCT is due to the loss of expression of HLA molecules

Therapeutical options for relapse management after HSCT

ANTI-LEUKEMIC THERAPY

Hypomethylating Agents

- Azacitidine
- Decitabine

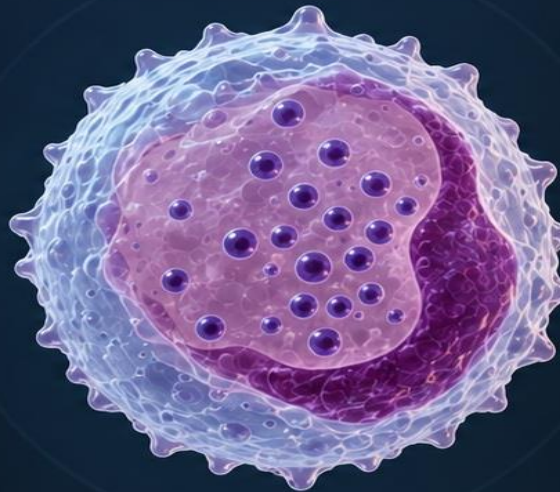
Target drugs

- FLT3 inhibitors
- IDH1/IDH2 inhibitors
- BCL2 inhibitors

Cytotoxic therapy

- Intensive chemotherapy
- Low-dose chemotherapy

Lenalidomide



IMMUNOTHERAPY

Second HSCT

Donor Lymphocytes Infusions

Checkpoint Inhibitors

- PD1/PD-L1 inhibitors
- CTLA4 inhibitors

Adoptive Immunotherapy

- CAR-T cells

DLI Key point



DIFFERENT
CLINICAL
STRATEGIES



TIMING



DOSE



DISEASE
SENSITIVITY



TOXICITY

DLI: Different Strategies for disease relapse control

PROPHYLACTIC

- ❑ High-risk disease (as defined by the European Leukaemia Net 2022 criteria)
- ❑ HSCT in advanced or refractory disease
- ❑ Ex-vivo lymphodepleted HSCT

Can be considered

- ❑ Non-myeloablative conditioning
- ❑ Absence of druggable targets (ie, FLT3)

PRE-EMPTIVE

Common practice

- ✓ Mixed chimerism
- ✓ Persistent minimal residual disease
- ✓ Molecular or cytogenetic relapse

Can be considered

- Infections

THERAPEUTIC

Common practice

- ❖ Haematological relapse
 - ❖ Extramedullary relapse
- Can be considered
- ❖ Post-transplantation lymphoproliferative disease

No disease

Molecular signal

Morphologic relapse

Current use of donor lymphocyte infusions after allogeneic stem cell transplantation in Europe: a survey on behalf of the cellular therapy and immunobiology working party of the EBMT

165 EBMT centers across 43 countries.

DLI use according to the indication and type of donor

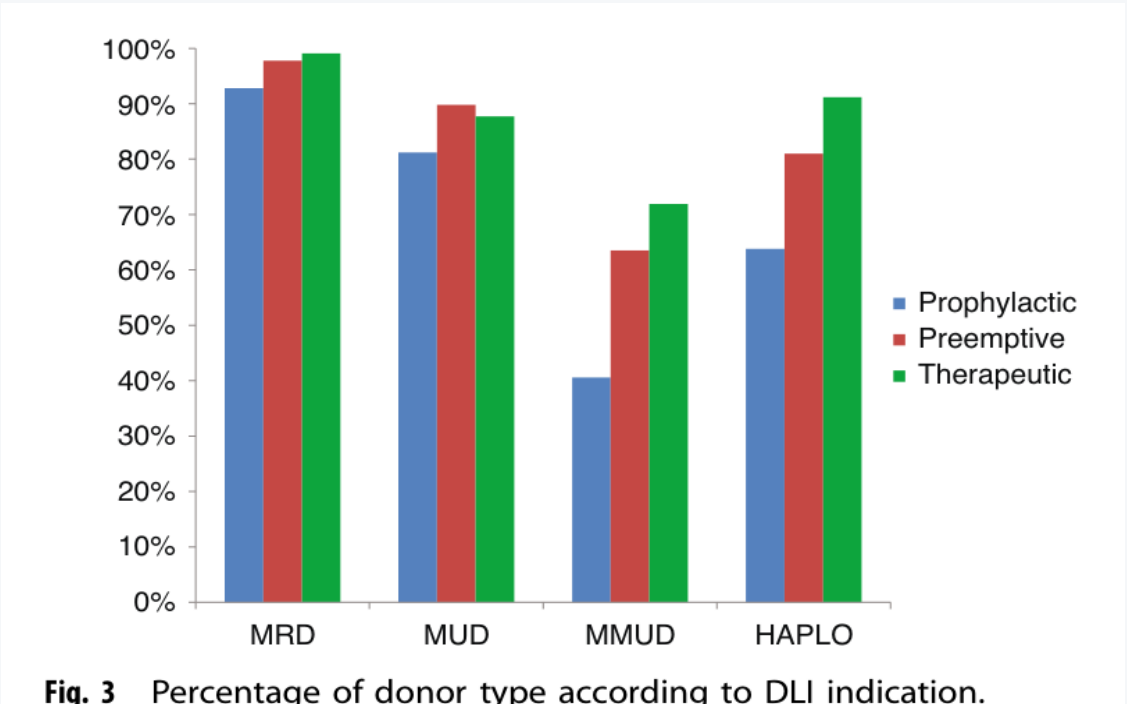
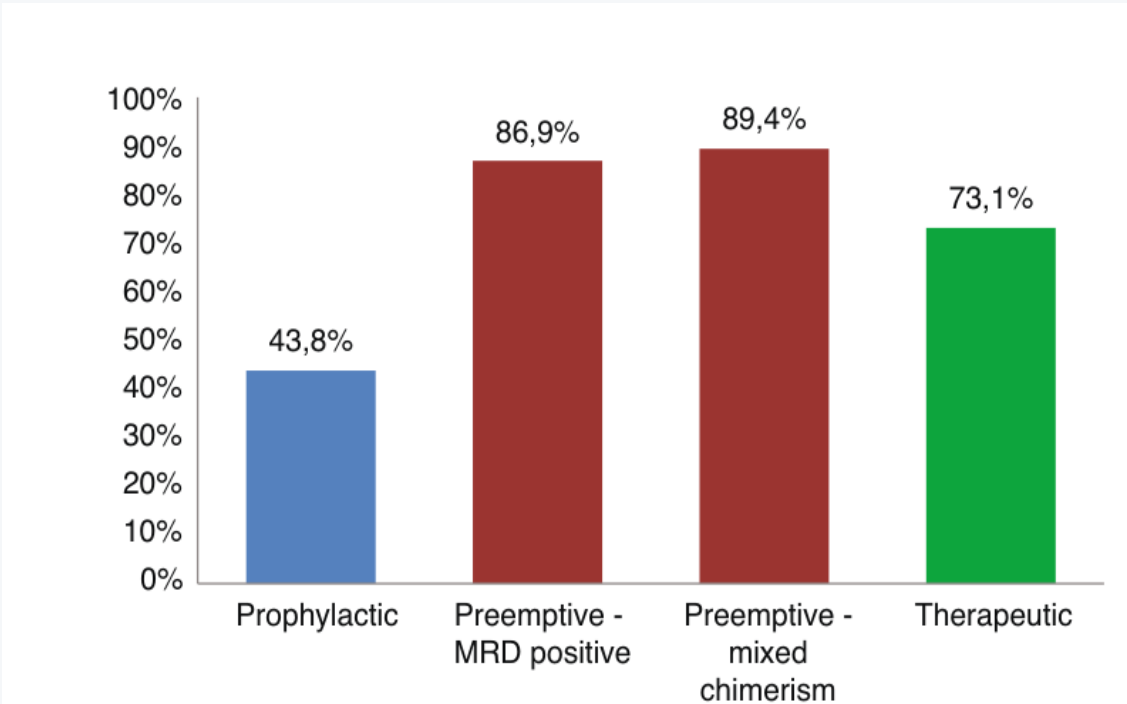
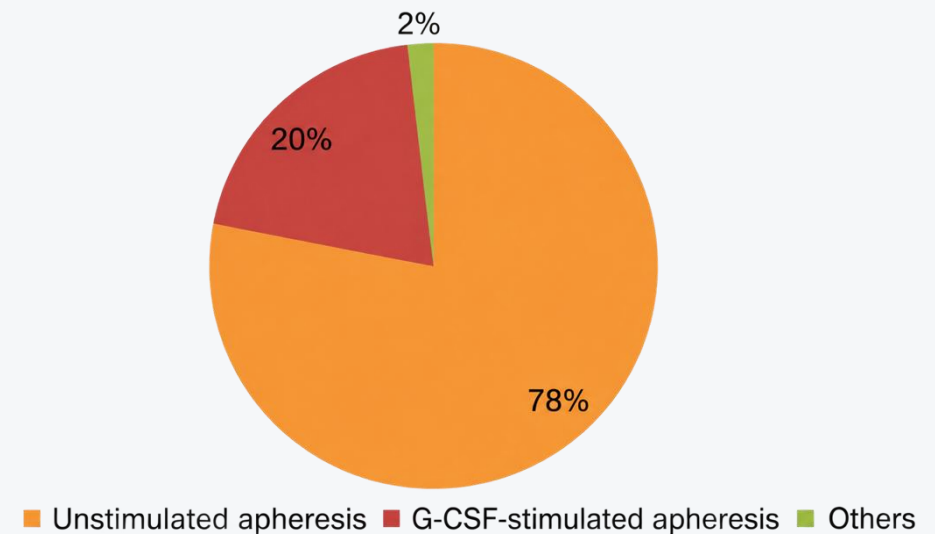
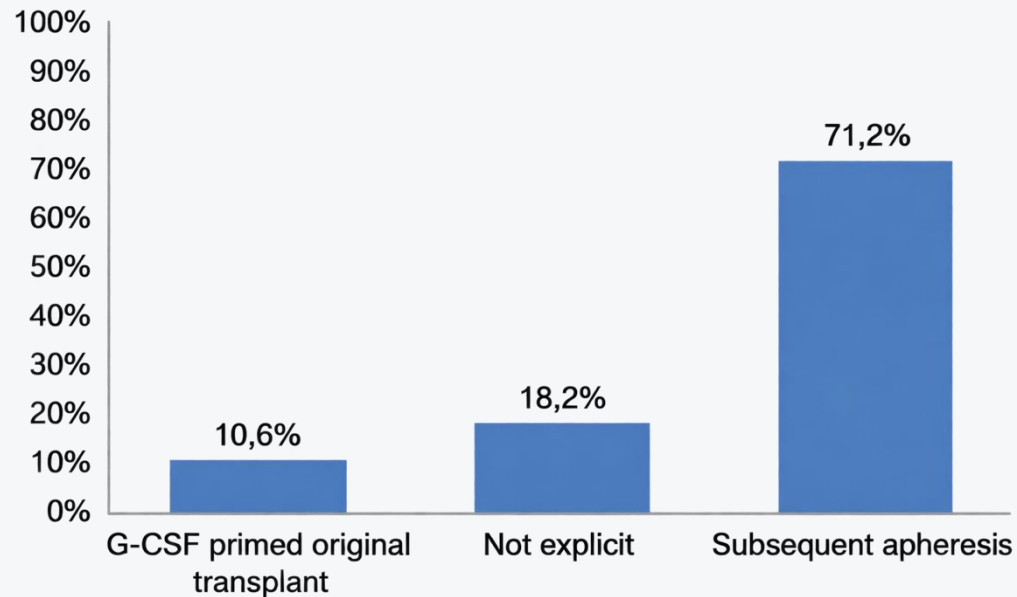


Fig. 3 Percentage of donor type according to DLI indication.

Current use of donor lymphocyte infusions after allogeneic stem cell transplantation in Europe: a survey on behalf of the cellular therapy and immunobiology working party of the EBMT

Practices used to collect DLI



- The first DLI dose as a fresh
- The other cryopreserved in different portions of either equal or escalating doses
- No substantial differences in outcomes between either of these two approaches

Why timing changes the tolerated dose

The transplant environment evolves over time



Earlier after HCT

More inflammation and residual host antigen-presenting cells → greater alloreactivity and GVHD risk.

Later after HCT

Tissue recovery and progressive donor immune replacement allow larger CD3+ doses to be used more safely.

Clinical consequence: dose cannot be interpreted without timing and type of donor.

Prophylactic , Pre-emptive and Therapeutic DLI Dose adjusted for Donor type and timing

	Recommended DLI dose for matched related donor	Recommended DLI dose for matched unrelated donor	Recommended DLI dose for mismatched unrelated donor or haploidentical donor	Number of DLIs
Prophylactic ⁴⁸⁻⁵⁰				
3 months (ex-vivo TCD: any risk; no ex-vivo TCD: high risk or refractory disease)	1×10^5 cells/kg	1×10^5 cells/kg	1×10^5 cells/kg*	1-3†
6 months‡	1×10^6 cells/kg	1×10^6 cells/kg	5×10^5 cells/kg	1-3†
Pre-emptive ^{51,52}				
3 months	$1-5 \times 10^5$ cells/kg	1×10^5 cells/kg	1×10^5 cells/kg	1-4§
6 months‡	$1-3 \times 10^6$ cells/kg	1×10^6 cells/kg	5×10^5 cells/kg	1-4§
Therapeutic ^{4,44,46,53}				
After systemic therapy¶	1×10^7 cells/kg	1×10^7 cells/kg	1×10^6 cells/kg	1-4

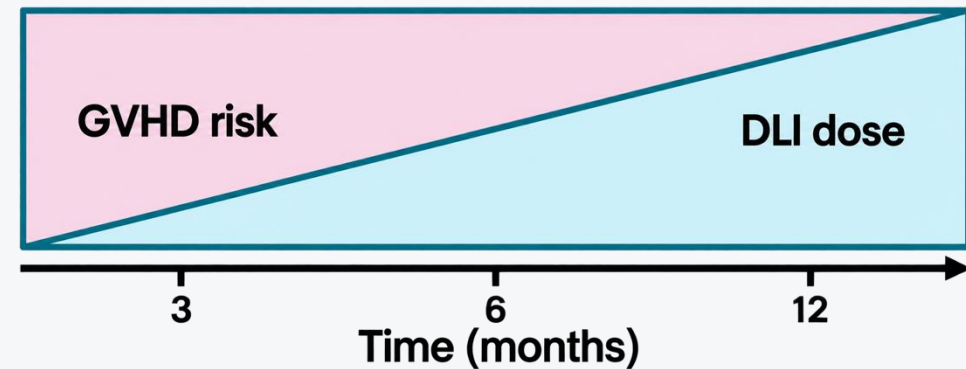
- The interval between two consecutive DLIs should be at least 4 weeks; DLIs in prophylactic settings should be at least 6 weeks
- The dose increase is generally of 0.5-1 log to max dose of 1×10^8 in therapeutic setting;
- The DLI therapy should be continued until MRD or CR or full chimerism has been reached without GVHD signs.

DLI Warning

Hematological toxicity

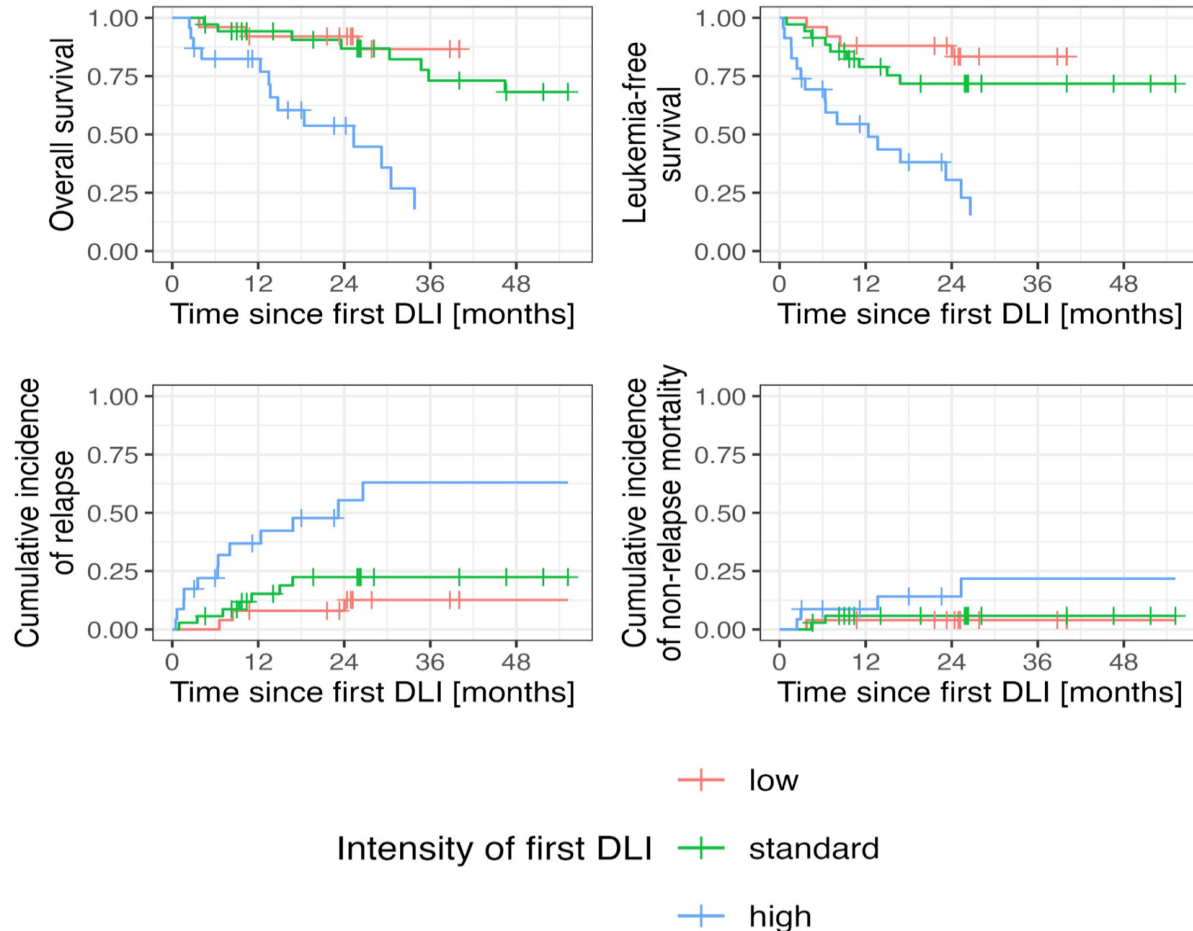
- ✓ Cytopenia from 1 day to 30 days after DLI are considered DLI related
- ✓ excluding all other possible causes eg, viral infections, drug induced cytopenias, disease recurrence, or clonal evolution, other systemic therapy as hypomethylating agents or tyrosine kinase inhibitors.

GVHD risk



- Donor type (> for MM donor)
- Cell dosage
- Timing (residual APC of the patient)
- Frequency of DLIs
- Interval between IS withdrawal
- Previous history of GVHD

Prophylactic and pre-emptive donor lymphocyte infusion in patients with acute myeloid leukemia and myelodysplastic syndrome: the high intensity model is not more effective



83 patients

36 proDLI

27 preDLI for

incomplete chimerism

20 preDLI MRD pos

42% of patients DLI standard intensity

30% DLI low intensity

28% DLI high intensity

Results: high-intensity DLI was the major risk factor for lower overall survival (hazard ratio [HR]=6.12), lower leukemia-free survival (HR=5.43), higher acute GvHD (HR=2.51), and lower treatment success (HR=0.41)

DLI outcomes after allogeneic HSCT



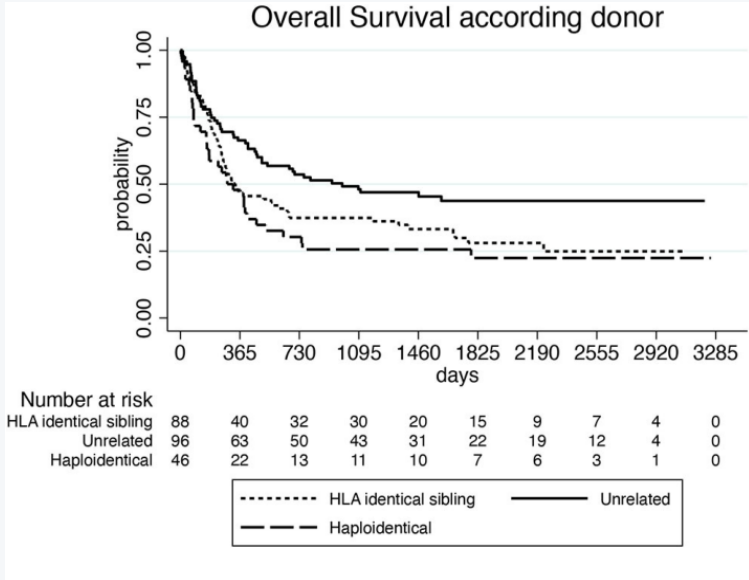
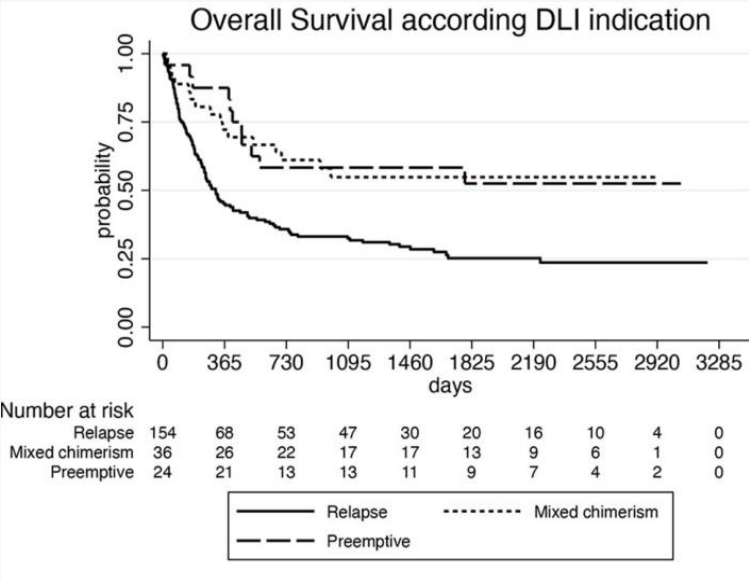
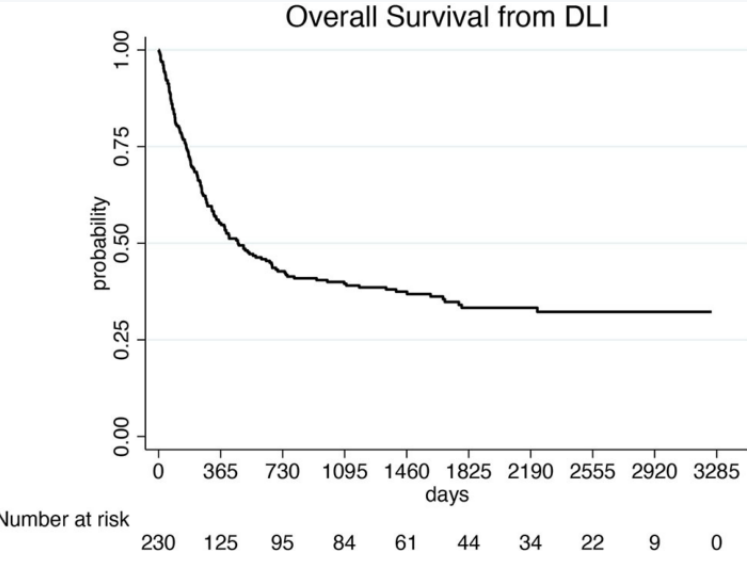
ORIGINAL RESEARCH
published: 15 October 2020
doi: 10.3389/fonc.2020.572918

Check for updates

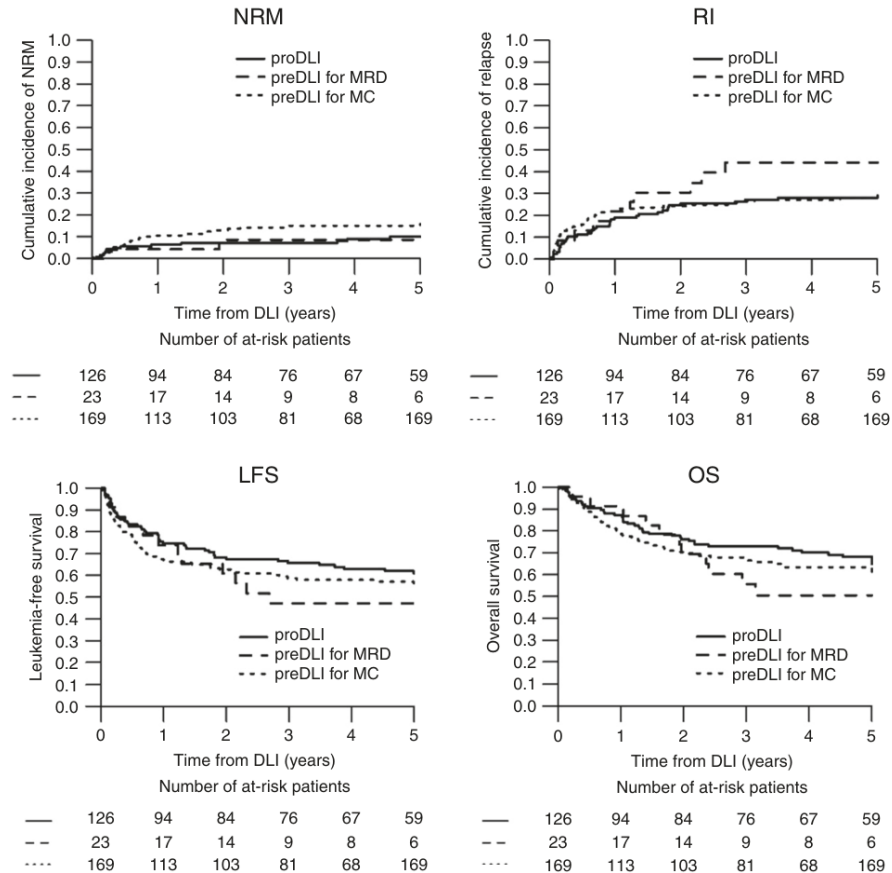
Donor Lymphocyte Infusions After Allogeneic Stem Cell Transplantation in Acute Leukemia: A Survey From the Gruppo Italiano Trapianto Midollo Osseo (GITMO)

Francesca Patriarca^{1,2*}, Alessandra Sperotto¹, Francesca Lorentino³, Elena Oldani⁴, Sonia Mammoliti⁵, Miriam Isola⁶, Alessandra Picardi⁷, William Arcese⁸, Giorgia Saporiti⁹, Roberto Sorasio¹⁰, Nicola Mordini¹⁰, Irene Cavattoni¹¹, Maurizio Musso¹², Carlo Borghero¹³, Caterina Micò⁴, Renato Fanin^{1,2}, Benedetto Bruno¹⁴, Fabio Ciceri³ and Francesca Bonifazi¹⁵

- 252 pts
- 180 Acute leukemias
- Relapse 73%
- mixed chimerism 17%
- pre-emptive/prophylactic use 10%



Long-term results and GvHD after prophylactic and preemptive donor lymphocyte infusion after allogeneic stem cell transplantation for acute leukemia



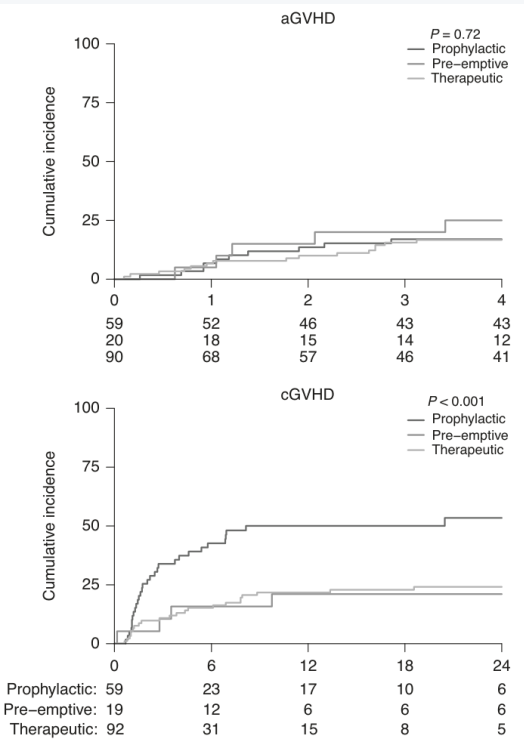
- 318 pts receiving DLI; as preemptive DLI for minimal residual disease (MRD, n = 23) or mixed chimerism (MC, n = 169) or Prophylaxis (proDLI, n = 126).
- Median interval from alloSCT to DLI1 was 176 days
- Cumulative incidences of acute graft-versus-host disease (aGvHD) grade II–IV°/chronic GvHD were 11.9%/31%.
- Nineteen patients (6%) died from DLI-induced GvHD.
- Age ≥ 60 years ($p = 0.046$), advanced stage at transplantation ($p = 0.003$), shorter interval from transplantation ($p = 0.018$), and prior aGvHD $\geq \text{II}^\circ$ ($p = 0.036$) were risk factors for DLI-induced GvHD.

DLI after haploidentical HSCT

ARTICLE

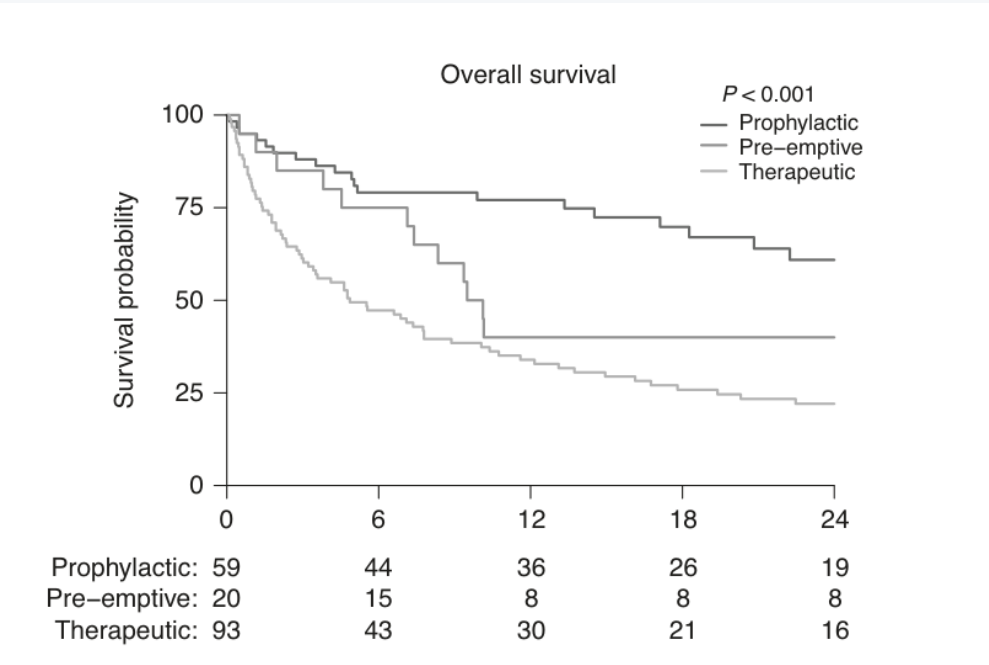
Donor lymphocyte infusions after haploidentical stem cell transplantation with PTCY: A study on behalf of the EBMT cellular therapy & immunobiology working party

Nicole Santoro^{1,2}, Jarl E. Mooyaart², Raynier Devillier³, Yener Koc⁴, Jan Vydra⁵, Luca Castagna⁶, Zafer Gülbaz⁷, José Díez Martín⁸, Mercedes Colorado Araujo⁹, Alexander Kulagin¹⁰, Mutlu Arat¹¹, Concepcion Herrera Arroyo¹², Maria Paola Martelli¹³, Mauro Di Ianni¹⁴, Jorinde D. Hoogenboom¹⁴, Liesbeth C. de Wreede¹⁵, Annalisa Ruggeri¹⁶ and Christian Chabannon¹⁷



- CI of grade II-IV aGVHD after DLI was low
- High incidence of cGVHD in the prophylaxis group.

- 173 patients who received one or multiple DLIs after haploHCT with (PTCY) at 47 EBMT centers from 2009 to 2018.
- DLI: prophylactic 34.3%, preemptive 11.6%, and therapeutic 54.1%



Survival and disease outcomes better in the early intervention

Disease sensitivity to DLI

VARIABLE ACTIVITY ACROSS HEMATOLOGIC MALIGNANCIES

LOW
SENSITIVITY

INTERMEDIATE
SENSITIVITY

HIGH
SENSITIVITY

B-cell ALL

TKIs, blinatumomab, CAR T-cells
DLI as remission consolidation

T-cell ALL

Decitabine, nelarabine, CD38 antibodies
DLI as remission consolidation

Diffuse large B-cell lymphoma

Ibrutinib (ABC type), CAR T-cells, bispecifics
DLI as remission consolidation

Acute myeloid leukaemia

Cytarabine, sorafenib, midostaurin, gilteritinib, other TKIs, hypomethylating agents, venetoclax
If loss of HLA-I, DLI not advised

Hodgkin lymphoma

Brentuximab vedotin
Consider checkpoint inhibitors as alternative to DLI due to risk of alloreactive complications

Chronic lymphocytic leukaemia

BTK inhibitors, venetoclax

Myeloproliferative neoplasms

Ruxolitinib, IFN- α
High risk of GVHD; consider lower DLI dose

Chronic myeloid leukaemia

TKIs, IFN- α

Follicular lymphoma

Anti-CD20, CAR T-cells, bispecifics
CAR T-cell therapy, bispecifics probably effective but data are scarce

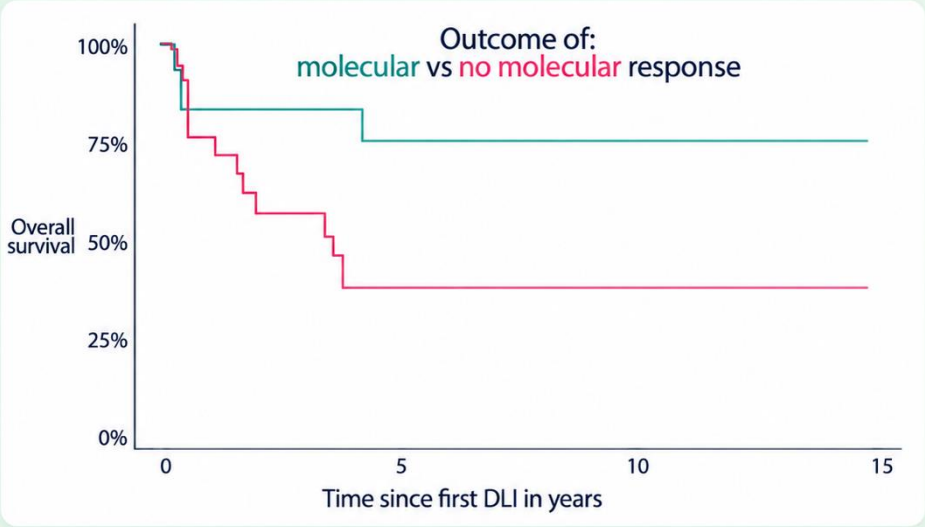
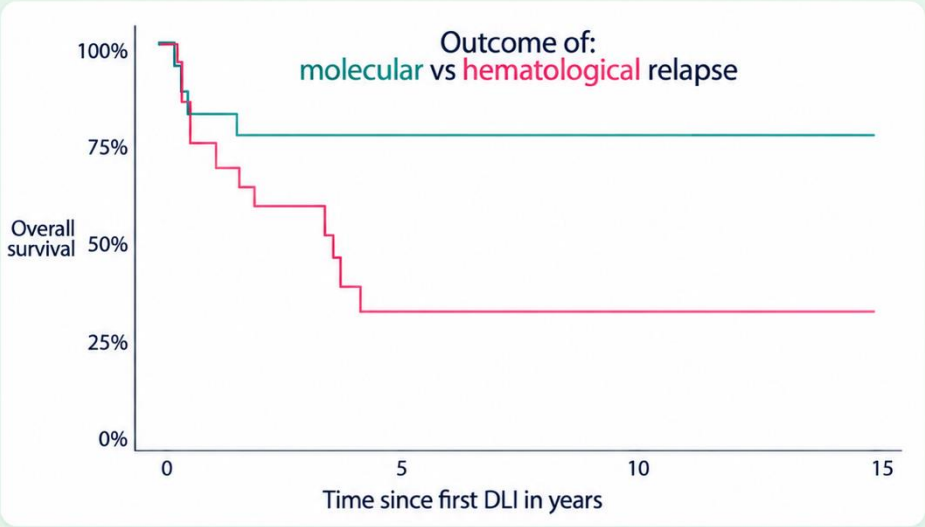
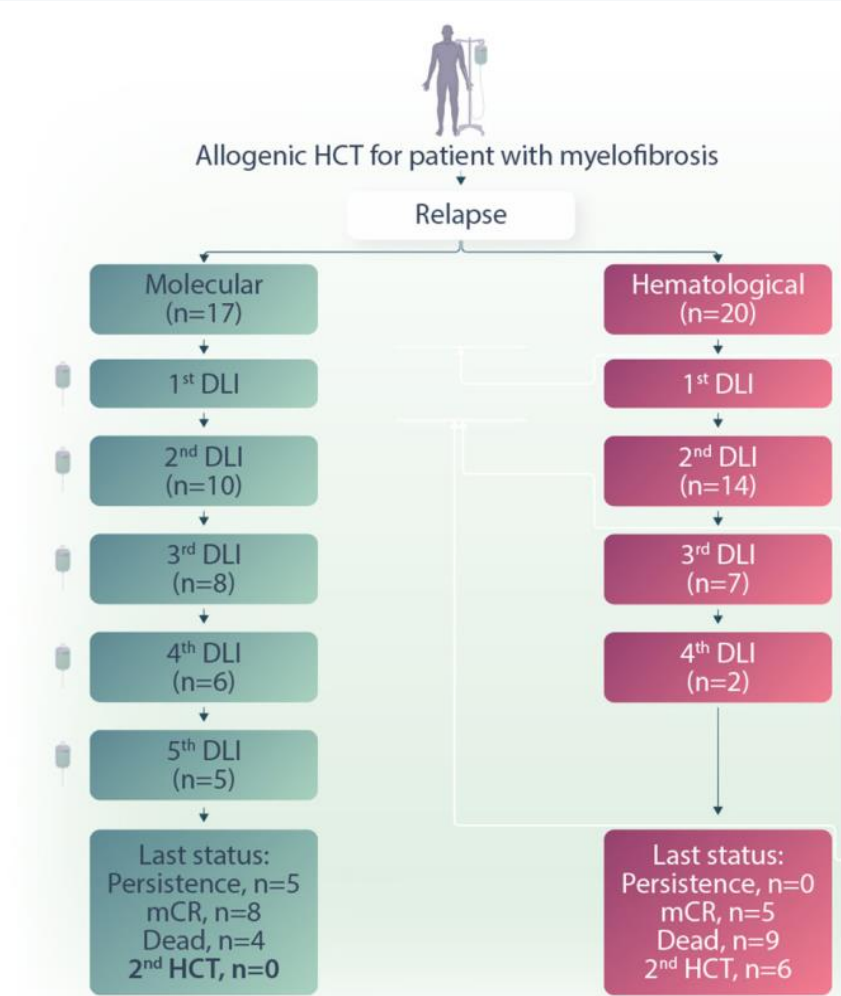
Mantle cell lymphoma

Ibrutinib, CAR T-cells

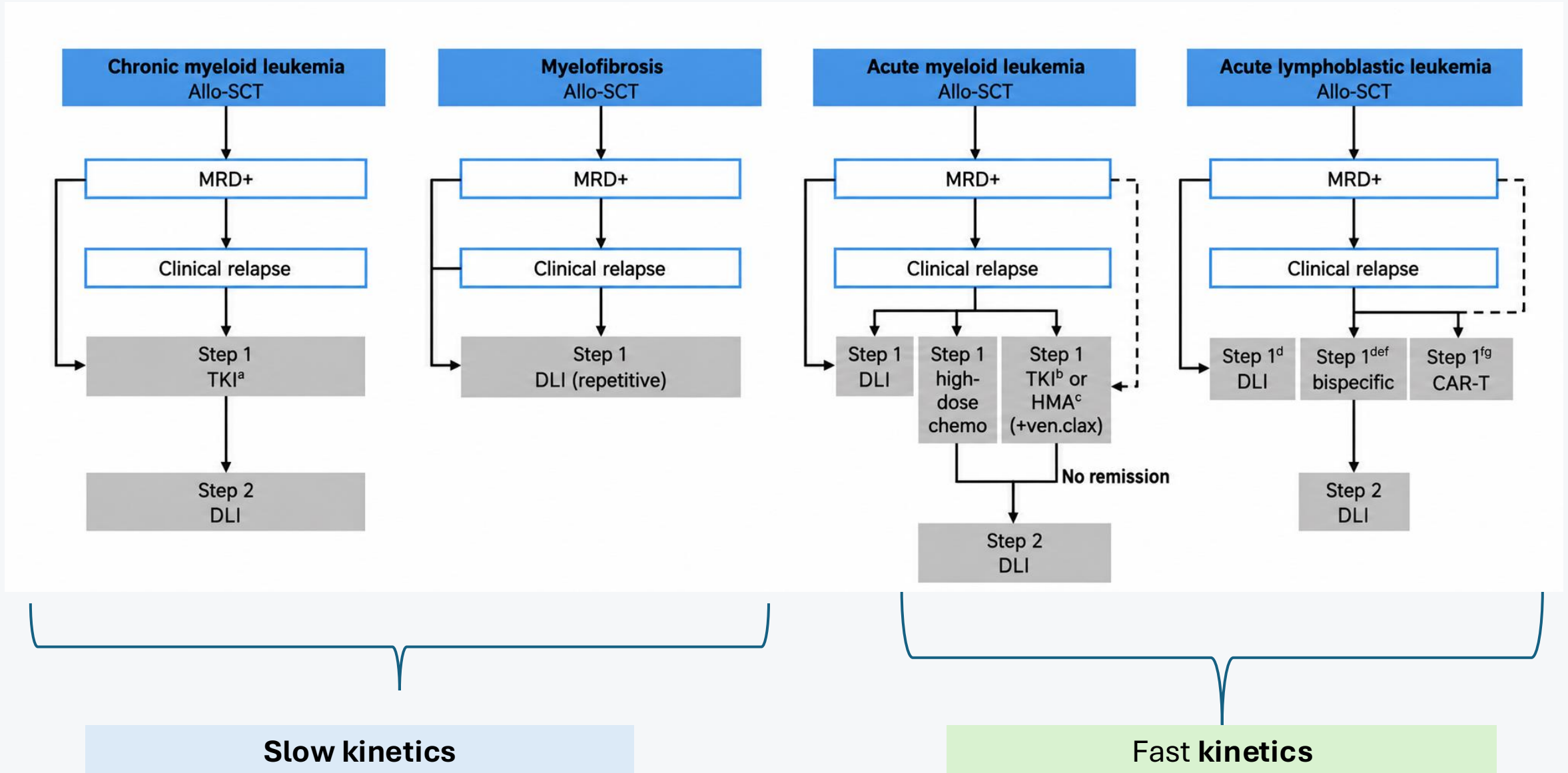
Multiple myeloma

Proteasome inhibitors, CAR T-cells, CD38 antibodies
High risk of GVHD in combination with lenalidomide

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



Different approach based on disease relapse kinetics



DLI: clinical evidence and treatment combinations

Annals of Hematology (2026) 105:213
<https://doi.org/10.1007/s00277-026-06973-7>

RESEARCH

Donor lymphocyte infusions for recurrence of myeloid neoplasms after allogeneic hematopoietic cell transplantation in the era of hypomethylating agents and BCL2 inhibitors

Miriam Mozaffari Jovein¹  · Thomas Meyer^{1,2} · Miguel Waterhouse¹ · Dietmar Pfeifer¹ · Jesús Duque-Afonso¹ · Michael Lübbert¹ · Kristina Maas-Bauer¹ · Ralph Wäsch¹ · Hartmut Bertz¹ · Justus Duyster¹ · Robert Zeiser^{1,3,4} · Jürgen Finke¹ · Claudia Wehr¹

Transplantation and Cellular Therapy 31 (2025) 26.e1–26.e13



Transplantation and
Cellular Therapy

journal homepage: www.astctjournal.org



Full Length Article
Allogeneic – Adult

Novel Drug Combinations and Donor Lymphocyte Infusions Allow Prolonged Disease Control in Multiple Myeloma Patients Relapsing after Allogeneic Transplantation

Chiara Nozzoli^{1,*}, Martina Pucillo², Luisa Giaccone³, Alessandro Rambaldi⁴, Maria Teresa Lupo Stanghellini⁵, Edoardo Benedetti⁶, Domenico Russo⁷, Nicola Mordini⁸, Silvia Mangiacavalli⁹, Paolo Bernasconi⁹, Matteo Parma¹⁰, Paola Carluccio¹¹, Piero Galieni¹², Paolo Rivela¹³, Massimo Martino¹⁴, Patrizia Chiusolo¹⁵, Miriam Isola¹⁶, Maria De Martino¹⁶, Elena Oldani⁴, Eliana Degrandi¹⁷, Riccardo Boncompagni¹, Elisabetta Antonioli¹⁸, Fabrizio Carnevale¹⁹, Monica Tozzi²⁰, Carmine Selleri²¹, Renato Fanin², Francesca Patriarca², on behalf of the Gruppo Italiano Trapianto Midollo Osseo (GITMO)

RESEARCH

Open Access

Salvage therapy containing sorafenib and donor lymphocyte infusion is associated with improved outcomes for FLT3 wild-type acute myeloid leukemia relapsing after allogeneic hematopoietic stem cell transplantation

Zhonghui Jiang^{1,2†}, Ya Zhou^{1,2†}, Yuxin Bai^{1,2†}, Fang Dai^{1,2†}, Menglin Fan^{1,2†}, Tian Zhang^{1,2†}, Danian Nie³, Yunxin Zeng⁴, Yiqiong Jiang⁵, Ping Zhu⁶, Zhiping Fan^{1,2}, Na Xu^{1,2}, Fen Huang^{1,2}, Ren Lin^{1,2}, Min Dai^{1,2}, Xiaojun Xu⁴, Zhangkun Li⁵, Hua Jin^{1,2}, Jing Sun^{1,2}, Qifa Liu^{1,2*} and Li Xuan^{1,2*}

Azacitidine, lenalidomide and donor lymphocyte infusions for relapse of myelodysplastic syndrome, acute myeloid leukemia and chronic myelomonocytic leukemia after allogeneic transplant: the Azalena-Trial

Thomas Schroeder,^{1,2} Matthias Stelljes,³ Maximilian Christopeit,⁴ Eva Esseling,⁵ Christoph Scheid,⁶ Jan-Henrik Mikesch,⁷ Christina Rautenberg,⁸ Paul Jäger,⁹ Ron-Patrick Cadeddu,⁷ Nadja Drusenheimer,⁸ Udo Holtick,¹ Stefan Klein,⁷ Rudolf Trenschei,¹ Rainer Haas,⁷ Ulrich Herming,² Nicolaus Kröger⁴ and Guido Kobbe⁷

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Received: December 28, 2022.
Accepted: May 23, 2023.

ARTICLE

Management of tyrosine kinase inhibitors and donor lymphocyte infusions post transplantation for chronic myeloid leukemia: a survey of contemporary practice on behalf of the chronic malignancies working party of the EBMT

Alexandros Kanellopoulos^{1,23}, Linda Koster², Hugues de Lavallade¹³, Guillermo Orti⁴, Sebastian Francis¹, Jakob Passweg¹⁵, Jane Apperley¹⁶, Wolfgang Bethge¹⁷, Werner Rabitsch⁸, Jennifer Clay⁹, Edouard Forcade¹⁰, Erin Hurst¹¹, Caroline Besley¹², Francesca Kinsella¹³, Mahmoud Aljurf¹⁴, He Huang¹⁵, Aloysius Ho¹⁶, Inken Hilgendorf¹⁷, Goda Choi¹⁸, Francis Ayuk¹⁹, Helbig Grzegorz²⁰, Matthias Stelljes²¹, Deborah Richardson²², Elena Morozova²³, Witold Prejzner²⁴, Robert Zeiser²⁵, Christopher Armstrong²⁶, Kavita Raj²⁷, Joanna Drozd-Sokolowska²⁸, Yves Chalandon²⁹ and Donal P. McLornan²⁷

Future Challenges

- DLI prospective studies
- Optimal integration into contemporary treatment algorithms
- Standardization of MRD methods
- How to best combine DLIs with targeted therapies for cytoreduction
- Assessing whether some agents might delay or eliminate the need for DLI

Quali sono i vantaggi dei DLI manipolati?