GIORNATE EMATOLOGICHE VICENTINE

X edizione

12-13 Ottobre 2023
Palazzo Bonin Longare - Vicenza

La prevenzione della malattia leucemica nell'adulto dopo trapianto

Enrico Maffini
U.O. Trapianto e Terapie cellulari Avanzate. Ist.Seragnoli. IRCCS Bologna

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
No disclosures							

Introduzione

- La ricaduta della neoplasia ematologica rappresenta la principale causa di fallimento del trapianto allogenico nella leucemia mieloide acuta.
- La terapia di salvataggio dei pazienti ricaduti post trapianto è inefficace e la prognosi generalmente infausta (2 year OS 15-25%)[1].
- Una terapia di «mantenimento/profilassi», definita come una terapia iniziata mentre il paziente è ancora in remissione completa, è un approccio promettente per ridurre il rischio di ricaduta post trapianto.
- La maggior parte delle ricadute si verifica entro 6-12 mesi, pertanto qualsiasi strategia di profilassi dovrebbe essere iniziata precocemente.

1 Schmid C, et al. Treatment, risk factors, and outcome of adults with relapsed AML after reduced intensity conditioning for allogeneic stem cell transplantation. Blood. 2012;119:1599–1606

Strategies to prevent Disease Relapse

- . Optimizing the antileukemic activity of the conditioning regimen
- . Early withdrawal of immune suppression
- . Donor lymphocyte infusion
- . Post-transplant maintenance therapy with targeted agents
- . Post-transplant maintenance with hypomethylating agents

Open questions

- **Quali pazienti beneficiano della profilassi?**
  - ✓ Rischio citogenetico/molecolare intrinseco
  - ✓ Status al trapianto e presenza/assenza di MRD
  - ✓ Intensità del regime di condizionamento
- **Quale strategia utilizzare?**
  - ✓ Sospensione precoce dell'immunosoppressione
  - ✓ Non target therapy
  - ✓ Target therapy
  - ✓ Immunoterapia cellulare (DLI profilattiche)
  - ✓ Condizionamento
- **Per quanto tempo?**

Open questions..

- Cosa fare se il paziente è peristentemente MRD positivo (NPM o IF) in corso di mantenimento?
- Cosa fare se il paziente rimane MRD positivo (NPM o IF) al termine del mantenimento?
- Quali sono I cut-off di MRD positività predittivi nel post trapianto?

There are consistent data demonstrating that MRD positivity by means of NPM1 (Nuclophosphmin-1)mutation (i.e. 100 to 1000 copies of mutated NPM1 per 10,000 ABL transcripts or 1% to 10% NPM1/ABL, respectively, is associated with a 60-90% risk of hematologic relapse.

1. Condizionamento

. Myeloablative fractionated busulfan-based conditioning regimen in patients with AML and MDS: Results of a randomized clinical trial comparing 2 fractionation schedules. Popat, et al. ASCO Meeting 2023 - NCT02250937

. Muffly L, et al. Preliminary data from a phase 1 study of JSP191 (Briquilimab), an anti-CD117 monoclonal antibody, in combination with low dose irradiation and fludarabine conditioning is well-tolerated, facilitates chimerism and clearance of minimal residual disease in older adults with MDS/AML undergoing allogeneic HCT. Presented at: 2022 Transplantation & Cellular Therapy Meetings

1. Condizionamento

. Phase I/II Study of Sorafenib Added to Busulfan and Fludarabine Conditioning Regimen in Patients With Relapsed/Refractory AML Undergoing Stem Cell Transplantation - NCT03247088

. Adding Venetoclax to fludarabine/busulfan RIC transplant for high-risk MDS and AML is feasible, safe, and active. Garcia, et al. Blood Adv (2021) 5 (24): 5536–5545. - The protocol was amended to separately assess the safety and efficacy of posttransplant maintenance therapy with hypomethylating agents and venetoclax following venetoclax plus FluBu2. NCT03613532

2. Early IS withdrawal

- A quali categorie di pazienti riservare il taper precoce dell'IS?

…..Rischio citogenetico sfavorevole secondo ELN 2017/2022

……Pazienti con malattia non in remissione al momento del trapianto

……Pazienti MRD+ pretrapianto che ricevono un condizionamento RIC

…..Pazienti in CR>=2

……Primary induction failure

- Qual è il timing ottimale di tapering e sospensione?
- Va differenziato in base al tipo di donatore?

3. Hypomethylating Agents

- PRO

✓ E’ applicabile a un maggior numero di pazienti rispetto alla terapia target

✓ Non esercita una pressione clone-selettiva, può conservare la sua efficacia a fronte della eterogeneità clonale della malattia che è in rapida evoluzione dopo il trapianto

- CONS

✓ Evidenze di efficacia meno forti

3. Hypomethylating Agents

- The value of maintenance therapy with hypomethylating agents (HMA) in the post-transplant setting has long been debated.

- 2022 European LeukemiaNet does not recommend subcutaneous azacytidine maintenance

3. Hypomethylating Agents

original reports

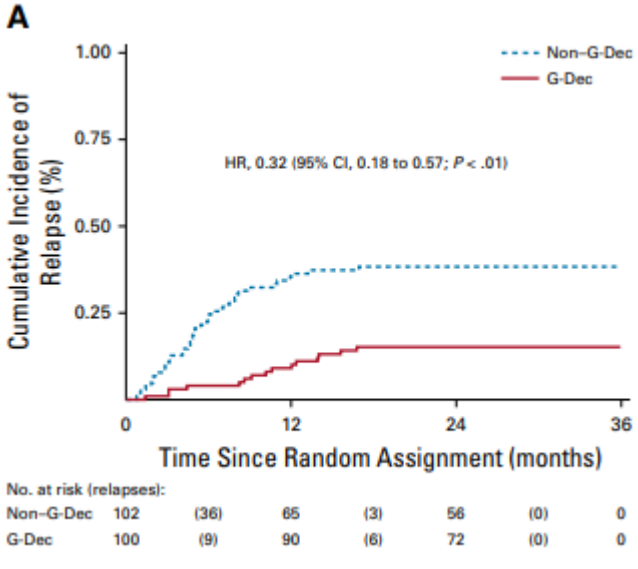
Effect of rhG-CSF Combined With Decitabine Prophylaxis on Relapse of Patients With High-Risk MRD-Negative AML After HSCT: An Open-Label, Multicenter, Randomized Controlled Trial

Lei Gao, MD, PhD[1]; Yanqi Zhang, PhD[2]; Sanbin Wang, MD, PhD[3]; Peiyan Kong, MD, PhD[1]; Yi Su, MM[4]; Jiong Hu, MD[5]; Ming Jiang, MD[6]; Hai Bai, MD[7]; Tao Lang, MD[8]; Jishi Wang, MD, PhD[9]; Li Liu, MD, PhD[10]; Tonghua Yang, MD[11]; Xiaobing Huang, MD[12]; Fang Liu, MD[4]; Shifeng Lou, MD[13]; Yao Liu, MD, PhD[1]; Cheng Zhang, MD, PhD[1]; Hong Liu, MM[1]; Li Gao, MD, PhD[1]; Jia Liu, MM[1]; Lidan Zhu, MM[1]; Qin Wen, PhD[1]; Ting Chen, MM[1]; Ping Wang, MM[1]; Jun Rao, MD[1]; Min Mao, MD[8]; Cunbang Wang, MD[7]; Xianlin Duan, MD[6]; Le Luo, MD, MM, MS[3]; Xiangui Peng, MM[1]; Kaniel Cassady, PhD[14]; Jiang F. Zhong, PhD[15]; and Xi Zhang, MD, PhD[1]

. phase II, open-label, multicenter, randomized controlled trial.
. 204 HR-AML who had received HCT 60-100 days before randomization, MRD-neg
. randomly assigned 1:1 to either rhG-CSF combined with minimal dose Dec (G-Dec group: 100 mg/m2 of rhG-CSF on days 0-5 and 5 mg/m2 of Dec on days 1-5) or no intervention (non–G-Dec group).

.The primary outcome was relapse after transplantation

3. Hypomethylating Agents



. 2-year RI in the G-Dec group was 15.0% (95% CI, 8.0% to 22.1%), compared with 38.3% (95% CI, 28.8% to 47.9%) in the non–G-Dec group (P , .01), with a hazard ratio (HR) of 0.32 (95% CI, 0.18 to 0.57; P , .01).

. No statistically significant difference between the G-Dec and non–G-Dec groups in the 2-year cumulative incidence of cGVHD without relapse 23.0% vs. 21.7%, with an HR of 1.07 (95% CI, 0.60 to 1.92; P 5 .81).

3. Hypomethylating Agents

A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients. Oran et al. Blood Adv 2021

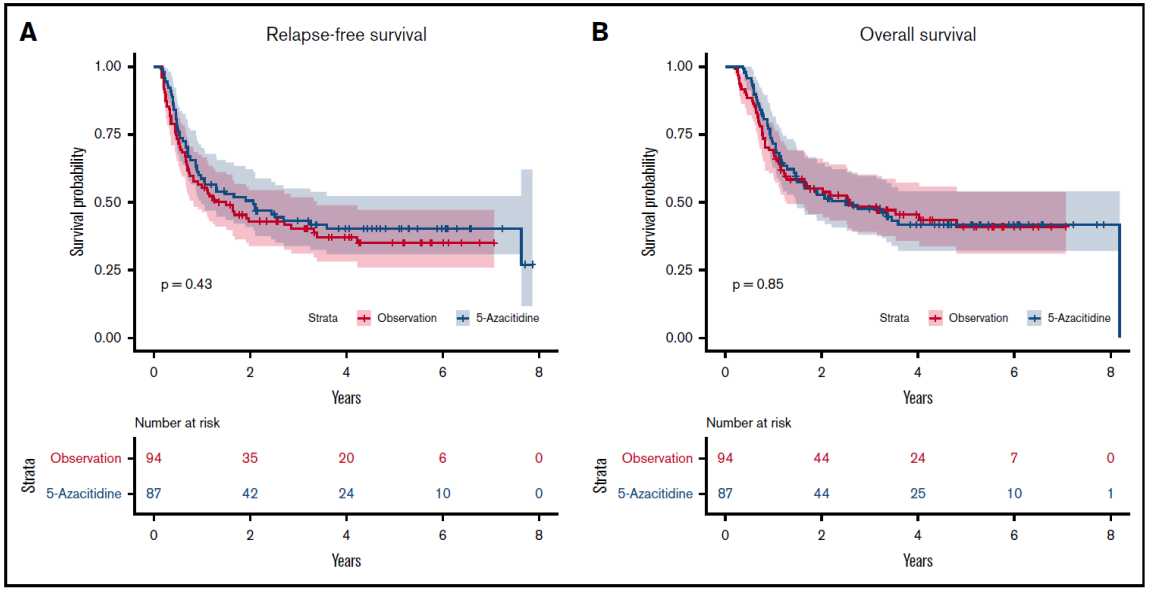
TABLE. Primary and Secondary Endpoints With Azacitidine Maintenance

	Azacitidine	Control	p Value
Survival outcomes			
Median relapse-free survival	2.07 years	1.28 years	0.43
Median overall survival	2.52 years	3.56 years	0.43
Relapse incidence at 1 year	41%	39%	Not available
Transplant-related mortality at 1 year	4.3%	5.3%	Not available
Graft-versus-host disease			
Grade 2-4 aGVHD at day 100	25.5%	28.7%	0.73
Grade 3-4 aGVHD at day 100	4.3%	2.1%	Not available
Chronic GVHD at 1 year	25.8%	30.8%	Not available

GVHD = graft-versus-host disease

The Phase III study by Oran et al. failed to meet its Primary endpoint.

3. Hypomethylating Agents



Perchè non si evidenzia un beneficio?

- ✓ Sopravvivenza inaspettatamente alta nel placebo?
- ✓ Molti withdrawal in corso di studio?

Solo il 27% dei pazienti ha completato 12 cicli, la mediana è stata 4.

- ✓ Dose troppo bassa? (32 mg/m2 x 5 days)

Oran et al. Blood Adv 2021

3. Hypomethylating Agents

Ci sono meta-analisi che analizzano la bontà dell'efficacia terapeutica degli ipometilanti nel post-trapianto?

3. Hypomethylating Agents

Maintenance With Hypomethylating Agents After Allogeneic Stem Cell Transplantation in Acute Myeloid Leukemia and Myelodysplastic Syndrome: A Systematic Review and Meta-Analysis. Kungwankiatticha et al. *Front Med*. 2022

The meta-analysis eligibility criteria were fulfilled by 14 studies. The overall survival and relapse-free survival of the HMA maintenance group were superior to the observation group, with a pooled risk ratio (RR) of 1.38 and 1.46, respectively. Moreover, the cumulative incidence of relapse was significantly lower in those who received HMAs.

3. Hypomethylating Agents

Conclusions: The current systematic review and meta-analysis illustrated that AML and MDS patients receiving HMA maintenance after allo-SCT had better outcomes in regards to OS, RFS, NRM, CIR as well as a reduced incidence of chronic GVHD

BUT…. meta-analysis in the context of post-transplant setting is still challenging and POTENTIALLY misleading!!

3. Hypomethylating Agents

. patients who died prematurely are by default in the control group without HMA due to a well-known statistical bias called “immortal time bias”.

. The elapsed time between allo-HCT and HMA initiation is an immortality period during which subjects who were candidate to receive HMA but died prematurely are counted as patients without HMA.

. the authors of the meta-analysis combined the outcomes of individual studies by pooling unadjusted risk ratio without accounting for confounding factors and without considering that the outcomes were censored events.

3. Hypomethylating Agents

Clinical Review & Education

JAMA Guide to Statistics and Methods

Immortal Time Bias in Observational Studies

Kabir Yadav, MDCM, MS, MSHS; Roger J. Lewis, MD, PhD

Research Article

Immortal Time Bias in Observational Studies of Time-to-Event Outcomes: Assessing Effects of Postmastectomy Radiation Therapy Using the National Cancer Database

Cancer Control
Volume 25: 1-7

DOI: 10.1177/1073274818789355
journals.sagepub.com/home/ccx
SAGE

3. Hypomethylating Agents

- Le principali tossicità riportate negli studi e riscontrate nella pratica clinica sono le citopenie: neutropenia e piastrinopenia in particolare.

  Among studies of HMA maintenance therapy, the most common >=3 grade AEs were thrombocytopenia, neutropenia and infection with median incidence rates of 35.1%, 35.1%, and 33.3% respectively.

- Le citopenie possono richiedere il delay del ciclo successivo.
- I demetilanti post trapianto non aumentano il tasso di GVHD acuta e cronica e la NRM.
- Sono realmente efficaci?

3. Hypomethylating Agents

- A quali categorie di pazienti riservare la profilassi con demetilanti?

…..Rischio citogenetico sfavorevole secondo ELN 2017/2022

……Pazienti con malattia non in remissione al momento del trapianto

……Pazienti MRD+ pretrapianto che ricevono un condizionamento RIC

……Primary induction failure

- Qual è la durata ottimale del mantenimento?

Negli studi con Ipometilanti il numero di cicli (di 28 giorni) varia da 6 a 12.

3. Hypomethylating Agents

- Trial clinici con ipometilanti in grado di darci qualche element in più, per decidere di utilizzarli o meno?
- Se si, in quale setting?
- Approcci combinatori?

3. Hypomethylating Agents

The randomized, double-blind, placebo-controlled phase III AMADEUS trial (NCT04173533) is currently ongoing to evaluate the efficacy of maintenance therapy with Oral-AZA in patients with MDS or AML post-HCT.

After transplant, patients receive Oral-AZA 200 mg or placebo on days 1 to 14 of each 28-day treatment cycle, for up to 12 cycles.

Patient stratification prior to randomization is based on conditioning intensity, age (< 60 or ≥ 60 y), and donor type (sibling or unrelated). The primary endpoint is RFS rate 1 year from randomization.

3. Hypomethylating Agents+Ven

Maintenance Therapy with Venetoclax/Azacitidine Can be Safely Given after Venetoclax/FluBu2 RIC Allogeneic Transplantation for the Treatment of High Risk MDS/AML: Results of a Phase 1 Study. Garcia et al. Blood 2022

. Between D42-D90, Ven+Aza maintenance therapy (Ven 400 mg on D1-D14 and Aza 36 mg/m2 IV on D1-D5) was initiated in pts who engrafted and had no evidence of morphologic relapse or uncontrolled GVHD in 42-day (dose level 1) or 28-day (dose level 2) cycles for up to 1 year.

. 27 pts enrolled (median age of 67y - range 47-78):
10 AML; 16 MDS
44% were flow MRD negative
56% had Ven exposure prior to HCT
Baseline *TP53*mut was present in 59%

3. Hypomethylating Agents+Ven

Maintenance Therapy with Venetoclax/Azacitidine Can be Safely Given after Venetoclax/FluBu2 RIC Allogeneic Transplantation for the Treatment of High Risk MDS/AML: Results of a Phase 1 Study. Garcia et al. Blood 2022

. 22 of 27 pts received VenAza maintenance therapy.
. Among 22 pts that received VenAza maintenance therapy, 1y PFS and 1y OS were 65% (95% CI: 40,82) and 79% (95% CI: 52,92), respectively
. Cumulative incidence of grade ≥2 acute GVHD at 6 mo was 22%, and chronic GVHD at 1y was 23%

. Pre-transplant flow MRD negativity was associated with improved 1y OS (88% vs 50%, *p*=0.03) and 1y PFS
. At time of HCT, NGS was positive in 89% (24/27), but this reduced to 42% (10/24) at D28 and 58% (14/24) at D100. PFS was similar for those with or without *TP53*mut at HCT

3. Hypomethylating Agents+Ven

Low-dose decitabine plus venetoclax is safe and effective as post-transplant maintenance therapy for high-risk acute myeloid leukemia and myelodysplastic syndrome. Wei, et al. 2021 Cancer Sci

. 20 AML/MDS high-risk patients were included in a prospective trial

. Decitabine was given at a dose of 15 mg/m^2 for 3 days and venetoclax at a dose of 200 mg daily for 21 days starting day +100 after transplantation.

. The 2-year OS and EFS were 85.2% and 84.7%, respectively.

. The 100-day acute and chronic GvHD rates were 55% and 20%, respectively.

. No grade ≥3 adverse events were observed

4. Target-therapy - FLT3

Mutations in FLT3 confer poor prognosis ofr AML patients, particulary those with ITD,as they have more frequent and earlier relapses. (Kottaridis et al Blood 2001; Pratcorona et al Blood 2013)

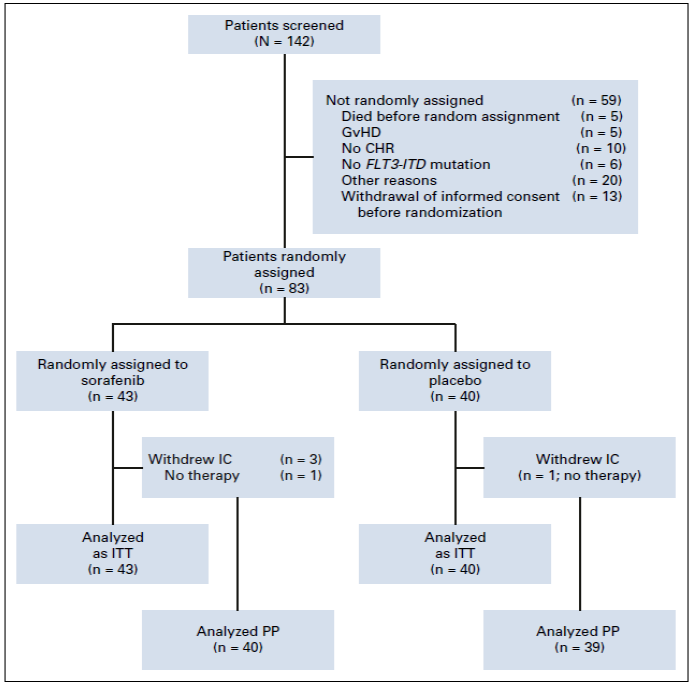
Relapse rates remain high still after allogeneic HCT.

Post-HCT maintenance therapy with TKI may improve outcomes in FLT3 mutated AML.

4. Target-therapy - FLT3

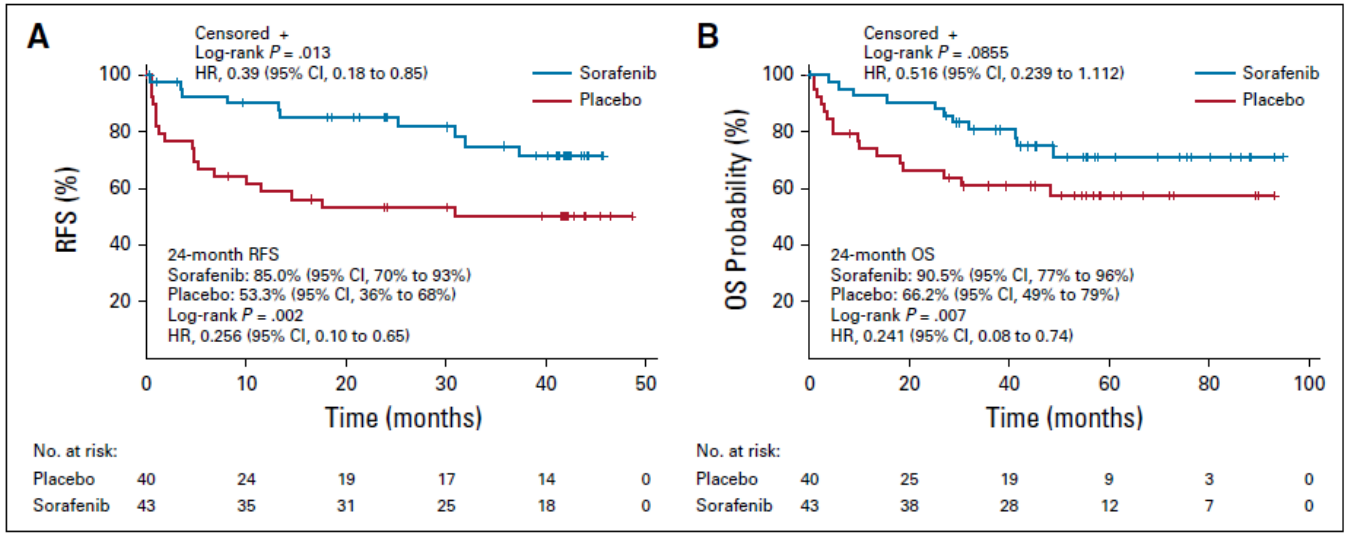
SORMAIN trial (German Clinical Trials Register: DRKS00000591), phase II randomized, placebo-controlled, double-blind. *Burchert* et al. JCO 2020

- Popolazione: 83 pazienti adulti (età 18-75, mediana 54) con LAM FLT3-ITD + in remissione completa post trapianto allogenico
- Study design: pazienti randomizzati 1:1 a ricevere Sorafenib (n=43) o placebo (n=40) per 24 mesi, iniziando tra il giorno +60 e +100 dopo trapianto
- Endpoint primario: Relapse Free Survival



4. Target-therapy - FLT3

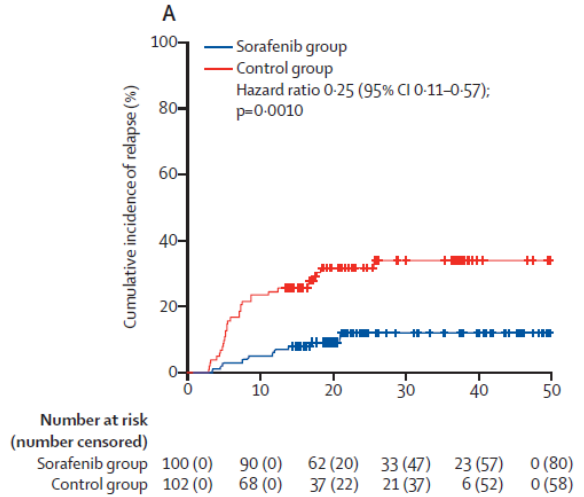
SORMAIN trial (German Clinical Trials Register: DRKS00000591), phase II



4. Target-therapy - FLT3

Xuan et al. Lancet 2020, phase III

- Popolazione: 202 pazienti adulti (età 26-43, mediana 35) con LAM FLT3-ITD + in remissione completa post trapianto allogenico
- Study design: Pazienti randomizzati a ricevere Sorafenib (n=100) vs non mantenimento (n=102) a partire dal giorno +30-+60 e fino al +180
- Endpoint primario: Incidenza cumulativa di ricaduta a 1 anno.



4. Target-therapy - FLT3

Xuan et al. Lancet 2023

Extended follow-up showed (Median FU 60.4 months):

. improved **OS**: 72% [95% CI 62·1-79·7] vs 55·9% [45·7-64·9]; p=0·011),

. extended **LFS**: 70% [60·0-78·0] vs 49% [39·0-58·3]; 0·47, 0·30-0·73; p=0·0007), and **GRFS** (58% [47·7-67·0] vs 39.2% [29·8-48·5]; 0·56, 0·38-0·83; p=0·0030),

. lower cumulative incidence of **Relapse** (15·0% [8·8-22·7] vs 36·3% [27·0-45·6]; 0·33, 0·18-0·60; p=0·0003)

. no increase in **NRM** (15·0% [8·8-22·7] vs 14·7% [8·6-22·3]; 0·79, 0·39-1·62; p=0·98) for patients in the sorafenib group

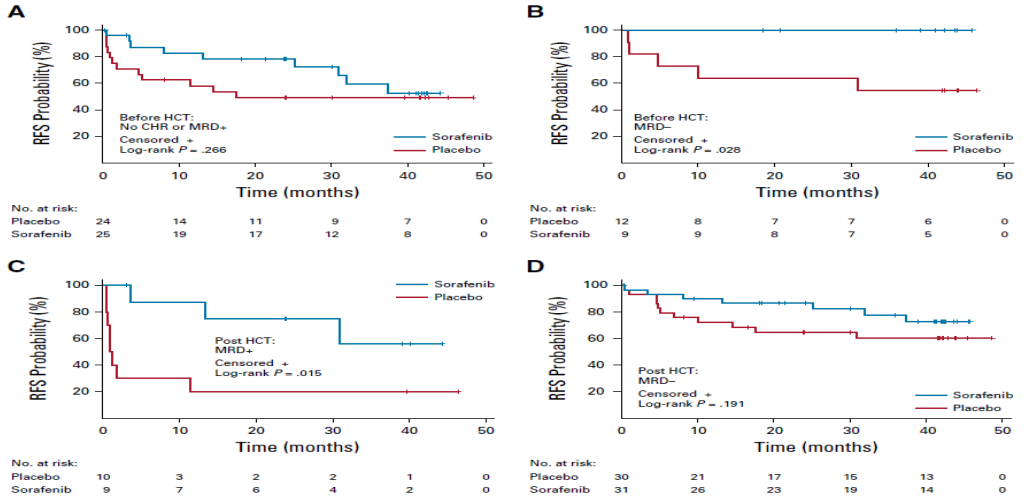
The 5-year follow-up results of our randomised phase 3 trial support the use of sorafenib maintenance post-transplantation as a standard of care for patients with *FLT3*-ITD acute myeloid leukaemia undergoing allogeneic HSCT.

4. Target-therapy - FLT3

- Qual è il beneficio del mantenimento con Sorafenib nei pazienti che hanno ricevuto midostaurina (o altri TKIs) pre-trapianto?

✓Solo 9 pazienti nel SORMAIN avevano ricevuto la Midostaurina in induzione….ma…..

✓I pazienti MRD- pre-trapianto ottengono I migliori risultati dal mantenimento



✓ E’ possibile che una terapia pre-trapianto con Chemio+Midostaurina, che aumenta la probabilità di remissioni complete MRD neg, sinergizzi con il Sorafenib di mantenimento nel migliorare l’outcome.

4. Target-therapy - FLT3

- Qual è il meccanismo d'azione principale del Sorafenib nel post trapianto: l'inibizione di FLT3-ITD o altre attività immuno-stimolatorie off-target?

- L'efficacia del Sorafenib può essere replicata e potenzialmente migliorata da inibitori più potenti e selettivi di FLT3 nel post trapianto?

. MIDOSTAURINA

. GILTERITINIB

4. Target-therapy - FLT3

. Nello studio RATIFY i pazienti sottoposti a trapianto allogenico di consolidamento della CR1 non continuano la **midostaurina** post-trapianto (non indicazione label nel post allogenico).

. In uno studio di fase II (AMLSG 16-10) midostaurina e chemioterapia intensiva, seguita da HCT e midostaurina single-agent come mantenimento ha dimostrato migliore EFS rispetto ai controlli storici (Schlenk,et al. Blood 2017).

. Nello studio RADIUS, randomizzato SOC vs SOC+ midostaurina (50 mg x 2/die) x 12 mesi post trapianto, c'è un trend di riduzione del rischio di ricaduta ma la RFS a 18 mesi non è risultata diversa tra i due bracci: 89% (69–96%) con midostaurina e 76% (54–88%) con SOC (HR, 0.46 [95% CI, 0.12–1.86]; P = 0.27), probabilmente per la scarsa numerosità del campione e la RFS inaspettatamente alta del gruppo di controllo. (Maziarz et al. 2021 BMT)

. Clinical trial (NCT03951961) – MAURITIUS Trial : Midostaurin in MRD Positive AML After Allogeneic Stem Cell Transplantation - Terminato x Insufficiente Reclutamento.

4. Target-therapy - FLT3

BMT-CTN 1506 MORPHO Trial - Gilteritinib

- Patients with FLT3-ITD–mutant AML, who were enrolled across 16 countries and 110 centers, must have had a morphologic first remission with only 1 or 2 induction treatments.
- Allogeneic transplant was conducted within 1 year of first response and any conditioning, donor, or graft-vs-host disease (GVHD) prophylaxis treatment was permitted.
- 356 patients were randomized to receive maintenance gilteritinib at 120 mg orally daily or placebo for 24 months
- 60% of patients received myeloablative conditioning therapy and 60% also received a FLT3 inhibitor before transplant.

BMT-CTN 1506 MORPHO Trial

- the study failed to reach its primary end point for RFS, in fact patients treated with gilteritinib achieved a numerical but not statistically significant improvement in RFS (HR, 0.679; 95% CI, 0.459-1.005; 2-sided P = .0518), The 2-year RFS rates were 77.2% with gilteritinib vs 69.9% with placebo, **BUT**…

- - Gilteritinib appears to have a benefit for the 50% of patients with detectable MRD pre- or post-transplant vs. those without detectable MRD. HR 0.51 favouring Gilteritinib vs. placebo (95% CI, 0.316-0.838; P=0.0065).
- - Gilteritinib resulted in 68.8% MRD eradication vs. 43.6% of placebo.
- RFS benefit with Gilteritinib was lower in MRD-negative disease patients (P= 0.57)

4. Target-therapy - FLT3

. Sorafenib è ancora il miglior TKI per il mantenimento?

Non ci sono studi di comparazione diretta Sorafenib vs Midostaurina/Gilteritinib

. Qual è la durata ottimale della terapia di mantentimento?

La durata del mantenimento differisce nei vari studi tra 6 mesi (Xuan et al.), 12 mesi (altri studi) e 24 mesi (SORMAIN trial).

. Concerns:

- Rischio di pressione selettiva e induzione di escape clones se il mantenimento dura troppo a lungo.

Of the 43 patients who relapsed, five of 11 assigned sorafenib and 17 of 32 allocated control had FLT3- ITD mutations; one patient assigned sorafenib acquired an FLT3 tyrosine kinase domain (FLT3-TKD) mutation at relapse. The other 20 patients were FLT3 wild-type at relapse. (Chinese trial)

- Rischio di ricadute tardive se il mantenimento dura troppo poco.

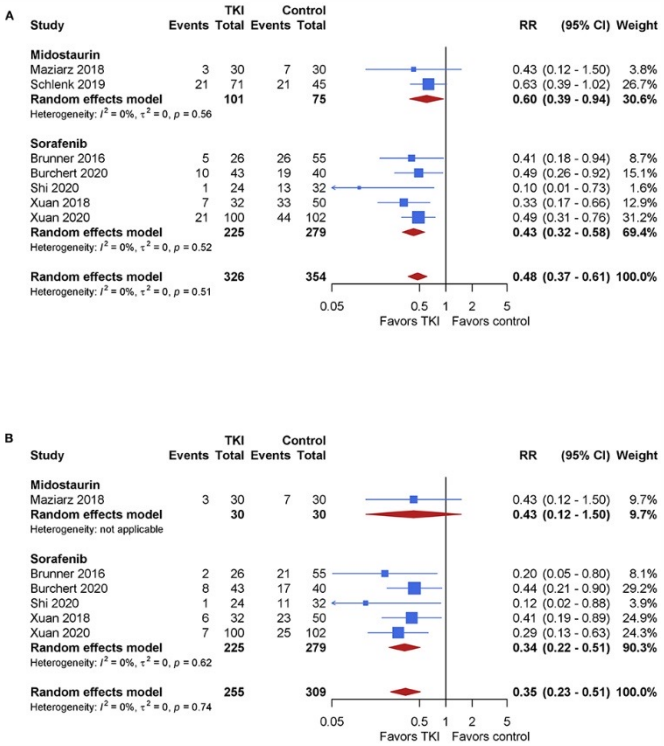
4 of 10 RFS events occurred after the end of sorafenib treatment and might be preventable by longer maintenance duration (SORMAIN).

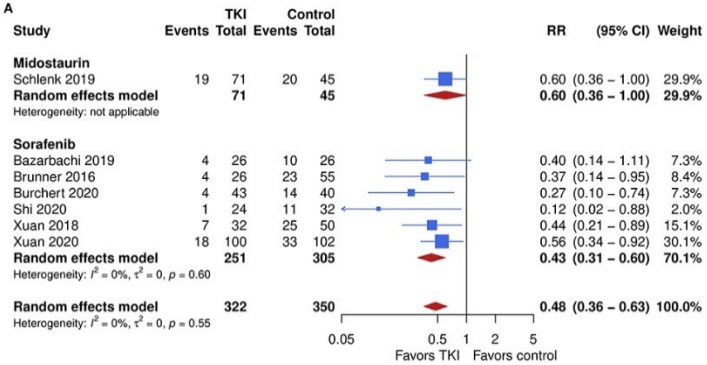
4. Target-therapy - FLT3

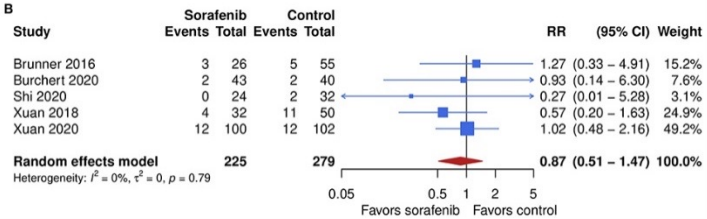
TKI Maintenance After Stem-Cell Transplantation for *FLT3*-ITD Positive Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis. Gagelmann et al. Front Imm 2021

. Meta-analysis comprising 7 studies comprising 680 patients were included. Five studies evaluated sorafenib and 2 studies evaluated midostaurin.
. relapse was significantly reduced after TKI therapy, showing an overall pooled risk ratio (RR) of 0.35 (95% confidence interval [CI], 0.23-0.51; $P < 0.001$), with a marked 65% reduced risk for RI
. overall pooled RR for relapse-free survival and overall survival showed significantly improved outcome after TKI maintenance therapy, being 0.48

4. Target-therapy - FLT3







4. Target-therapy – IDH

- Ivosidenib & Enasidenib both effectively inhibit R-2-hydroxyglutarate and can restore normal myeloid differentiation.

- In large multicenter phase 1/2 studies, these agents have demonstrated favorable toxicity profiles and the ability to induce durable remissions both alone and in combination with other therapies in both relapsed/refractory and newly diagnosed AML.

- Ivosidenib and enasidenib have received regulatory approval from the US FDA for the treatment of IDH1- and IDH2-mutated AML.

- Several trials are ongoing to test IDH inhibition efficiency at preventing AML relapse (NCT03515512; NCT03728335; NCT04522895; NCT03564821)

4. Target-therapy – p53 Reactivator

- - Eprenetapopt/Azacitidine Maintenance After Allogeneic HSCT for TP53-Mutant AML and MDS – Mishra A, et al.

- - Phase II, multicenter, open-label trial to assess efficacy and safety of eprenetapopt combined with azacitidine as maintenance therapy after HCT
- - Patients with mTP53 MDS or AML received up to 12 cycles of eprenetapopt 3.7 g once daily intravenously on days 1-4 and azacitidine 36 mg/m2 once daily intravenously/subcutaneously on days 1-5 in 28-day cycles.
- - Median RFS was 12.5 months (95% CI, 9.6 to not estimable) and the 1-year RFS probability was 59.9%

5. DLI

- PROS

✓Alcune evidenze di efficacia nella LAM ad alto rischio citogenetico

A registry-based matched-pair analysis evaluated the efficacy of prophylactic donor lymphocyte infusion (proDLI).

Adults receiving proDLI in complete remission (CR) and controls were pair-matched for age, diagnosis, cytogenetics, stage, donor, gender, conditioning and T-cell depletion.

Eighty-nine pairs were identified (median follow-up: 6.9 years).

Within the entire cohort, no difference was observed.

However, among patients with high-risk acute myeloid leukaemia (AML) (unfavourable cytogenetics and/or transplanted beyond first CR), proDLI recipients had improved overall survival (69.8% vs. 40.2% in controls, P = 0.027).

ProDLI has moderate efficacy but can contribute to improved outcome in high-risk AML.

5. DLI

- CONS/LIMITAZIONI DI APPLICABILITA’

✓Rischio di GVHD acuta e cronica, anche severa

✓Il rischio di GVHD è tanto maggiore quanto più precocemente vengono applicate (a parità di altri fattori, quali il tipo di donatore)

✓Possono essere applicate a partire dal +90/+100, in associazione a un taper precoce dell’IS, in pazienti senza GVHD acuta, senza infezioni e off immunosuppression (da almeno 1 mese) →NON prevengono le ricadute precocissime

✓La schedula di somministrazione non è standardizzata

Conclusioni

- La profilassi della ricaduta post trapianto rimane ad oggi di primaria importanza nella LAM ad alto rischio per la prognosi sfavorevole dei pazienti che ricadono.
- Non ci sono evidenze forti né trial randomizzati al di fuori del contesto della LAM FLT3-ITD+ e del Sorafenib, il cui uso resta ancora off-label.
- La precoce sospensione dell'immunosoppressione e l'immunoterapia rappresentano le strategie più promettenti.
- È necessario uno sforzo collegiale per produrre dati di efficacia e sicurezza più robusti e per una migliore stratificazione dei pazienti che possono beneficiarne.
- E' da chiarire in quali pazienti una strategia profilattica sia superiore a una strategia pre-emptive MRD-driven.

Grazie per l'attenzione

Enrico Maffini,

U.O. Trapianto e Terapie cellulari Avanzate. Ist.Seragnoli. IRCCS Bologna