EHA-GBMTA-AHA Hematology Tutorial:

Clinical Case – [Acute Myeloid leukemia]

18-20.10.2024 A.Sevoyan

Nothing to disclose

Patient History

- Patient 23-year-old male was admitted at Hamatology Center on March 2020 with complains of fatigue, fever, pain in the legs, and gingival hyperplasia.
- No history of other diseases.
- Cholecystectomy in 2016.
- No history of medication use.

Laboratory and other diagnostic examination results

- **CBC:** HB-130g/l, RBC–4.63×10^{12}/L, MCV-82.1fl, MCH-28.1pg, MCHC-342g/dl, Plt.–27.0×10^{9}/L, WBC –43.26×10^{9}/L, Blast cells-78%, Myel.-3%, Banded cells-2%, Neut-6%, Eos-1%, Lymph.-8%, Mon-2%.

- **Biochemistry examination results:** LDG-1781U/L.

- **USD:** Liver size-18.6x8.0cm, Spleen-16cm. Kidney sizes within normal ranges. Lymph nodes cervical, submandibular-1.2x0.5cm

Laboratory examination results

- **Immunophenotyping:** CD13-86%, CD33-89%, CD34-98%, CD117-45%, CD38-98%, CD64-neg, HLA-DR-93%, CD3-neg, MPO-neg, CD79a-neg. Conclusion 78% of blast cells of myeloid origin were detected.
- **Cytogenetic examination results.** Presence of del(5q), del(7q), 20q, PML-RARα, MLL(11;23q), *CBFβ/YMYH11* were not found.
- **Molecular genetic analysis.** *FLT*-ITD was not detected (Laboratory of genetic technologies Russian federation)
- **Diagnosis: Acute Myeloid leukemia**

Treatment: Induction chemotherapy Cytarabine+Daunorubicin

Patient received 1st induction chemotherapy scheme «7+3» (03.2020)

- Complications: Fever, clostridium difficile. Fever was continued with no response to antibiotics and clostridium difficile treatment.
- QuantiFERON test and entero-colonography revealed Crohn’s disease.
- Histological examination of biopsy specimen approved the Crohn’s disease.
- Metylprednisolone 48mg was prescribed, temperature and general condition were normalized.

Treatment outcomes

- **CBC:** HB-132g/L, RBC–4.33×10^{12}/L, MCV-88.5fl, MCH-30.1pg, MCHC-34.5g/dl, Plt.–166.0×10^{9}/L, WBC–6.97×10^{9}/L, Blast cells-7%, Myel.-3%, Metam.-2%, Banded cells-4%, Neut-45%, Lymph.-30%, Mon-9%.

- **Bone marrow aspiration, day 29:** Blast cells -32%.

- 2nd course of CT scheme 7+3 with mitoxantrone was administrated.

- (No matched donor, absence of ASCT in Armenia 2020).

- **CBC, day 28:** Blast. cells-16%
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- **Bone marrow aspiration, day 28.** Blast cells-9% were detected.

Treatment continuation, Belorussia 25.06-13.07.2020

- **FLAG-IDA** chemotherapy scheme was administrated.
- **Bone marrow aspiration 27.07.2020.** Blast cells-10%

- **Immunophenotyping 27.07.2020:** 26% blast cell with the following phenotype brigh+CD33 brigh+CD15 brigh+CD13dim±CD117±CD34 ±

- Salvage therapy was suggested. Parents refused patients to underwent suggested therapy.

- Returned to Armenia, palliative course with hydroxycarbamide + purinethol was initiated.

- **Worsening of general condition 08-09.2020.**

Chemotherapy CLARA (09-10.2020) Armenia

CBC on day 26 HB-126g/l, RBC–4.30×10^{12}/L, Plt.–95.0×10^{9}/l, WBC –22.6×10^{9}/l, Myel.-1%, Metam.-1%, Banded cells-14%, Neut-74%, Lymph.-3%, Mon-3%.

Bone marrow aspiration on day 26. Blast cells -1%, Prom-0.5%, Myel.-13%, Metam.-13.5%, Banded cells-16.5%, Neut-29.5%, Pronormoblast-1.5%, Normoblast bas.-5.5%, polychrome-19%. Bone marrow is cellular.

Immunophenotyping CD13-34%, CD15-94%, CD64-71%, CD10-51%. 96% of neutrophils and 1% of lymphocytes. **No blast cells were detected.**

18.10.2020 patient went to Italy Azienda Ospedaliera di Perugia for ASCT

CLARA, combination treatment of clofarabine and cytarabine

Azienda Ospedaliera Di Perugia, Italy 20.10.2020

21.10.2020
Complete hematological remission confirmed.

20.11.2020

CBC: Increased WBC number, blast cells 72%, the following immunophenotype CD34+, CD33+, CD117+/-, CD13+/-.

Bone marrow biopsy: 80-90% blast cells. Immunohistochemistry CD34+mpo10+, PGM1-, CD56-, Glycophorin C-, LAT-, CD3-, CD79a-, BcL2+.

Bone marrow aspirate immunophenotype: CD45+ (71,8%) CD34+CD33+dim, CD38+, HLA-DR+CD117+/-(73%)CD11b+/-(77%),CD13+/-(68%).

Cytogenetics: 48XY,+8,+13 in 90% of analyzed metaphases

Molecular genetics: FLT3-positive

Treatment continuation, Italy 11.2020

- Cytoreductive therapy cytarabine 200mg/m2 3 days+ venetoclax
- Conditioning therapy
- Total marrow irradiation-Total lymphoid irradiation (TMI-TLI), total dose 20 Gy
- Tiotepa 3,75mg/kg -10, -9
- Fludarabine 30mg/m2 days -10 until – 6
- CTX (Cyclophosphamide) 15mg/kg days -8,-7
- Following infusion Treg lymphocytes, then T-cons lymphocytes
- Infusion allogeneic stem cells transplantation from haplo-identic donor (father) 24.12.20

Complications. Mild oral gastrointestinal mucositis grade II-III. Acute GVHD grade III. Received methyprednisone 2mg/kg.

Response to treatment

26.01.2020 Bone marrow biopsy. Variable cellularity. Granulopesis is prevalent with the normal hematopietic precursors (CD34+). Erythropoiesis Glycophorin C+ with the forms E1/E2. Moderate increase of megakaryocytes number (LAT+). Monocytopesis (PGM1+) 5% with mature elements. Blast cells were not observed. Complete hematological remission.

22.02.21. Complete donor chimerism.
23.03.21. Comlete donor chimerism.
20.04.21. Complete donor chimerism. No FLT-ITD mutation.
19.05.21. Complete donor chimerism.
22.06.21. Complete donor chimerism. No FLT-ITD mutation.
14.07.21. Complete donor chimerism. No FLT-ITD mutation.
Mantainance therapy with Sorafenib 200mg daily 06.2021

Follow-up

2023 patient free of sorafenib

Went to USA and under follow up in USA.

Patient is still in complete hematological remission.

Discussion

The major factor of successful treatment results and disease-free survival for this patient

- Novel strategy of HLA haploidentical ASCT combines age adapted myeloablative conditioning with regulatory and conventional T cell adoptive immunotherapy?
- Maintenance therapy with Sorafenib?
- Both together?

References:

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4. Franco Aversa[1*], Antonio Pierini[2], Loredana Ruggeri[2]. The Evolution of T Cell Depleted Haploidentical Transplantation. Front. Immunol., 27 November 2019. Sec. Alloimmunity and Transplantation. Volume 10 - 2019

Treg/Tcon Immunotherapy and High Dose Marrow Irradiation Ensure Full Control of Leukemia Relapse in Haploidentical Transplantation

Antonio Pierini, MD, PhD[1] · Alessandra Carotti, MD[2] · Loredana Ruggeri, MD, PhD[1].

ASTCT **375**Volume 25, Issue 3, Supplement S264-S265March 2019

Abstract. Allogeneic hematopoietic stem cell transplantation (HSCT) is the most powerful therapy for patients with high risk of relapse. In spite of that, no matter the donor source or conditioning regimen used, leukemia relapse is still the leading cause of HSCT failure. In HLA-haploidentical HSCT, we recently applied a clinical protocol consisting of total body irradiation (TBI)-based conditioning regimen and a peripheral blood CD34+ cell graft combined with the adoptive transfer of naturally occurring regulatory T cells (Tregs) and conventional T cells (Tcons). No post-transplant pharmacologic GvHD prophylaxis was given. Such protocol was associated with low GvHD and relapse rate (Martelli et al., Blood 2014). To further reduce leukemia relapse in Treg/Tcon-based haploidentical HSCT (Treg/Tcon haplo-HSCT) we used high dose hyper-fractionated TBI (HF-TBI) in the conditioning regimen. We also extended Treg/Tcon haplo-HSCT to patients that are unfit (because of previous comorbidities) and/or too old to withstand high intensity regimens. In these patients the extra-hematologic toxicity of irradiation was reduced with the use of targeted total marrow and lymph node irradiation (TMLI).

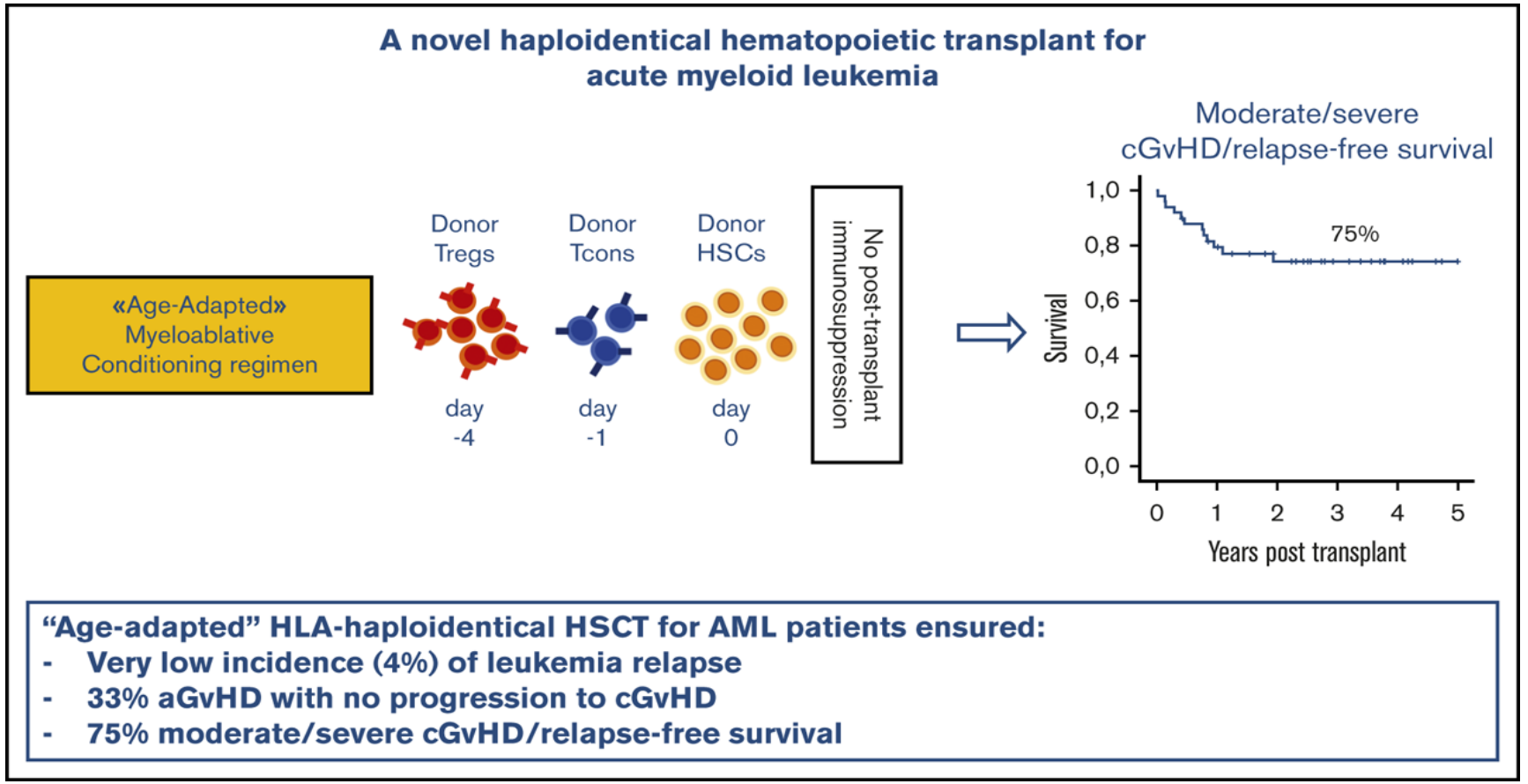
Tregs prevent GVHD and promote immune reconstitution in HLA-haploidentical transplantation

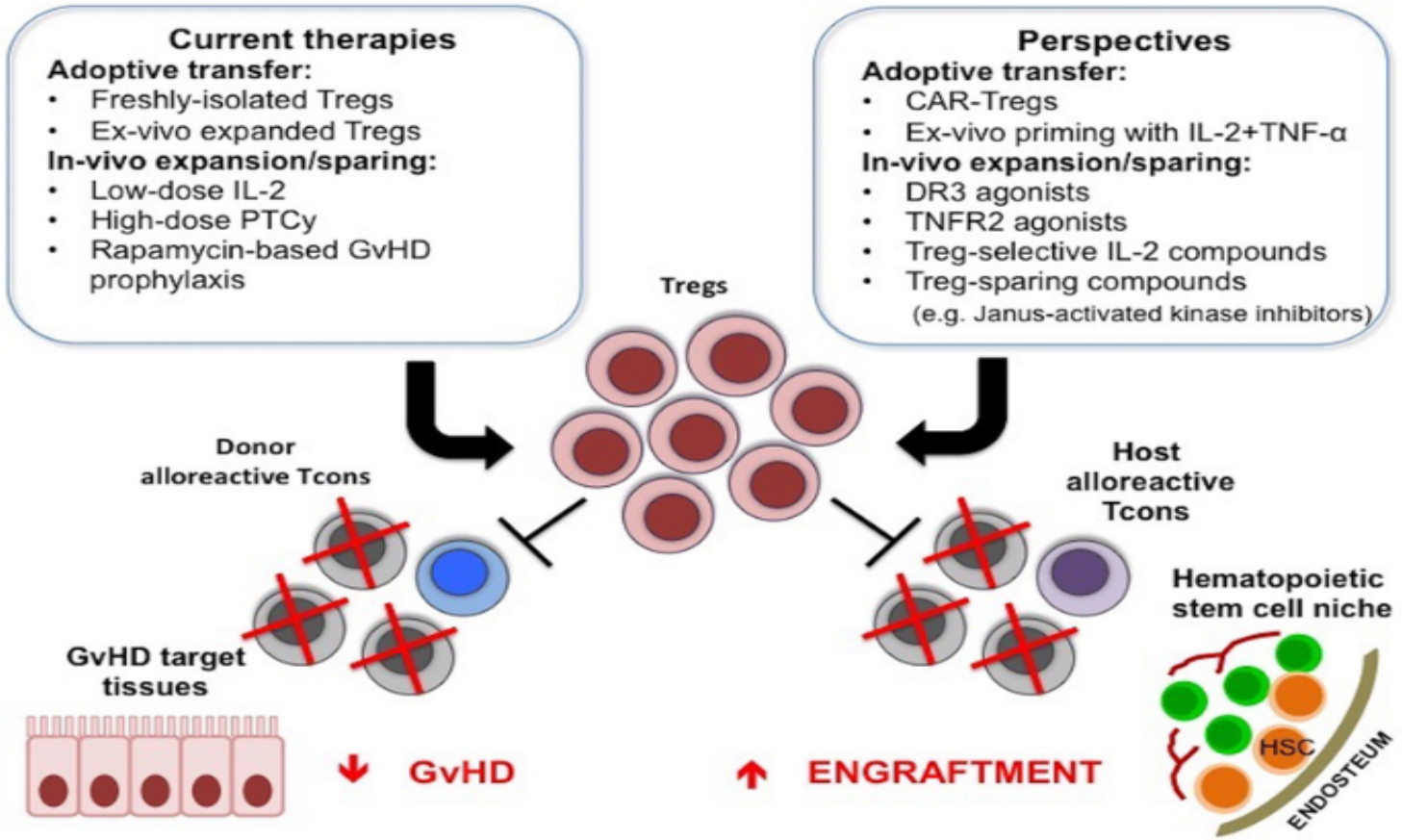
Mauro Di Ianni, Franca Falzetti, Alessandra Carotti,

Blood (2011) 117 (14): 3921–3928.

Abstract. Hastening posttransplantation immune reconstitution is a key challenge in human leukocyte antigen (HLA)–haploidentical hematopoietic stem-cell transplantation (HSCT). In experimental models of mismatched HSCT, T-regulatory cells (Tregs) when coinfused with conventional T cells (Tcons) favored posttransplantation immune reconstitution and prevented lethal graft-versus-host disease (GVHD). In the present study, we evaluated the impact of early infusion of Tregs, followed by Tcons, on GVHD prevention and immunologic reconstitution in 28 patients with high-risk hematologic malignancies who underwent HLA-haploidentical HSCT. We show for the first time in humans that adoptive transfer of Tregs prevented GVHD in the absence of any posttransplantation immunosuppression, promoted lymphoid reconstitution, improved immunity to opportunistic pathogens, and did not weaken the graft-versus-leukemia effect. This study provides evidence that Tregs are a conserved mechanism in humans.

Haploidentical age-adapted myeloablative transplant and regulatory and effector T cells for acute myeloid leukemia





Treg-based therapies in allogeneic HCT. Adoptive transfer of Tregs or the use of compounds that can favor their function in vivo are used to promote donor engraftment and protect from GvHD after HCT. New strategies to further enhance in vivo efficacy of Treg-based therapies are under active investigation, and include CAR-Tregs, ex-vivo priming with IL-2 and TNF-α, TNFR2, or DR3 agonists, Treg-selective IL-2 compounds or compounds that inhibit Tcon function while sparing Treg suppressive activity.

Thank you for your attention

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