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SOCIETA' ITALIANA
TALASSEMIE ED EMOGLOBINOPATIE

COLLANA SCIENTIFICA SITE
OPINIONE DI ESPERTI

SELECTING β-THALASSEMIA PATIENTS FOR GENE THERAPY: A DECISION-MAKING ALGORITHM

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Note for users

This document is the full version of the SITE Experts' Opinion and can be downloaded from the SITE website at www.site-italia.org

The members of the panel have signed the Declaration of Conflicts of Interest.

INTRODUCTION

The Società Italiana Talassemie ed Emoglobinopatie (Italian Society of Thalassemias and Hemoglobinopathies, SITE) has responded to the need to develop this document which is the result of an “Expert Opinion” to describe the inclusion and exclusion criteria, and clinical priority to identify which patients with transfusion-dependent beta-thalassemia (β-TDT) could benefit from gene therapy (GT).

The methodology has been formulated on the basis of an evaluation of currently available scientific evidence, using validated criteria that have, however, been interpreted with particular care given the limited experience acquired with the registered trials, since a conventional treatment is available for this pathology and that this product availability will be, at least initially, quite limited.

Still today, the only curative and most widely used therapy for β-TDT is allogeneic transplantation of hematopoietic stem cells. However, recent trials in GT seem to offer very promising results in terms of overall survival and thalassemia-free survival, and are opening up a new landscape of treatment.

The experience of allogeneic transplantation in β-TDT, begun in 1981, had immediately showed the importance of patient risk stratification in order to achieve the best results. (See the Pesaro experience and their classification of patients according to risk.) Data in the literature and the recent analysis of these by the European Registry of Hemoglobinopathies on a large number of patients (2011 and 2018 analyses) confirm that patient age (<14 years) and an HLA identical family member offer the best outcome from allogeneic transplantation.

Current knowledge and data of non-conventional treatments, such as allogeneic transplantation and gene therapy, are discussed in order to identify the best available treatment and indication for these patients according to their characteristics.

At this particular moment, that seems to foresee the emergence of “the age of GT”, it is essential to establish the patient “setting” in which this can be applied, or better, the one which can represent a true and proper indication, and the clinical priority for access to the procedure.

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CONTENT

The document is presented as a dynamic, up-datable tool.

Content has been organized in such a way as to allow consultation on two different levels: an interactive Flow Chart (see Figure) showing the different clinical problems discussed with practical conclusions on each chapter providing detailed information on each aspect of the subject.

METHODS

The decisional algorithm has been developed as part of the scientific activity of SITE that has defined the feasibility of the project and selected the multi-disciplinary group of experts in hemoglobinopathies and/or transplantation to draw up the related clinical problems.

The document has been prepared for specialists in the centers of the National Network of Hemoglobinopathies.

Published literature (Medline, PubMed, Embase, Cochrane Library) has been searched for concrete evidence of the best candidates for allogeneic transplantation who should not undergo GT. Keywords used were: Beta-Thalassemia; Bone Marrow Transplantation; Gene Therapy; Hematopoietic Stem Cell Transplantation; Hemoglobinopathies; Hepatitis; Iron Overload; Liver Complications; Endocrine Complications. Evaluation of the literature and scientific evidence have been reported and discussed through phone conferences and by email. The final revision was carried out by a pool of external reviewers who have evaluated the clinical relevance, applicability, and legal status of the document, and the cohesion between the recommendations and the summaries of the tests produced to test the algorithm.

The final version of the document will be uploaded onto the SITE web site (www.site-italia.org). The results of the procedures will be collected in the clinical electronic database used by the centers (eg: Webthal®, International Health Repository) to carry out stratification.

Regarding this, the group would like to emphasize the approach used for evaluating β-TDT patients' access to GT. Until a few decades ago, β-TDT was considered an unfavorable pathology. Today, β-TDT has an open prognosis thanks to the conventional treatment that has transformed it into a chronic disease.

Given this change, it has been decided, in this first phase of access to GT, to give the priority to patients in the best clinical condition who, as shown in the allogeneic transplantation setting, are those who will obtain the best results with the least risk. This cautious approach is due to the limited experience obtained with the registered trials and also to the probable limited availability of the product used, at least initially. The defined priority criteria could vary in the light of new scientific evidence. Given this, the document is to be considered dynamic and up-datable .

RESULTS AND CONCLUSIONS

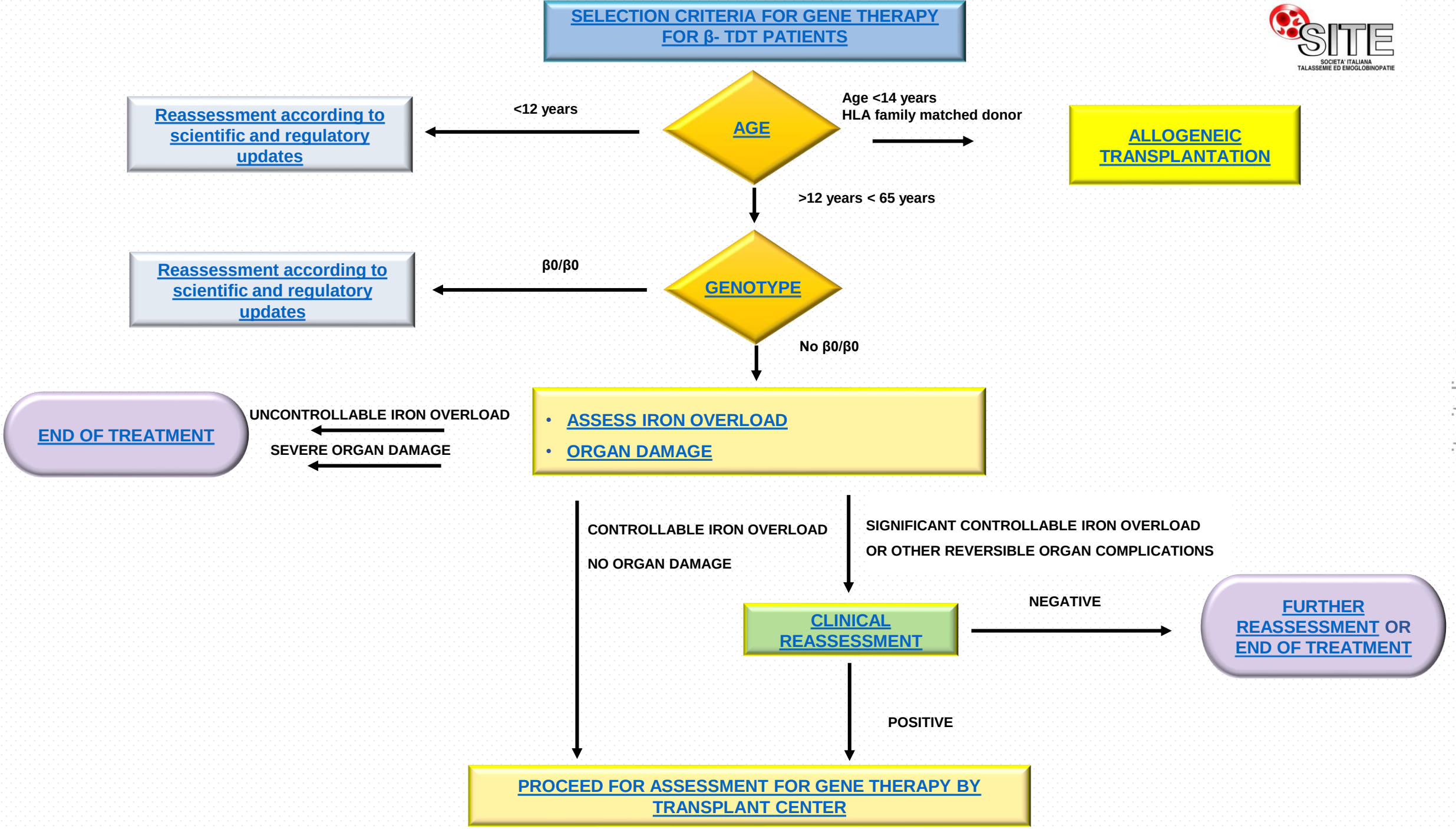
Patient's selection must be carried out through a consensus decision between the Center of the Italian Network of Hemoglobinopathies and the treatment center qualified to carry out HSC transplantation.

In consideration of the appropriate controls, patients must absolutely not be considered suitable in cases of:

- fulfilling exclusion criteria indicated by the regulatory authorities (see EMA / CHMP / 166977/2019);
- uncontrollable iron overload and/or chronic organ damage (e.g. pulmonary hypertension).

Controllable iron overload requires reassessment. Caution must be exercised when assessing patients with complications and comorbidities.

Access to GT must be reassessed according to scientific and regulatory updates.


SELECTION CRITERIA FOR GENE THERAPY FOR β- TDT PATIENTS
AGE
<12 years
Reassessment according to scientific and regulatory updates
Age <14 years
HLA family matched donor
ALLOGENEIC TRANSPLANTATION
>12 years < 65 years
GENOTYPE
β0/β0
Reassessment according to scientific and regulatory updates
No β0/β0
ASSESS IRON OVERLOAD
ORGAN DAMAGE
UNCONTROLLABLE IRON OVERLOAD
SEVERE ORGAN DAMAGE
END OF TREATMENT
CONTROLLABLE IRON OVERLOAD
NO ORGAN DAMAGE
SIGNIFICANT CONTROLLABLE IRON OVERLOAD
OR OTHER REVERSIBLE ORGAN COMPLICATIONS
CLINICAL REASSESSMENT
NEGATIVE
FURTHER REASSESSMENT OR END OF TREATMENT
POSITIVE
PROCEED FOR ASSESSMENT FOR GENE THERAPY BY TRANSPLANT CENTER
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CH.1- REQUIREMENTS FOR SUITABILITY OF β-TDT PATIENTS FOR GT

Suitable patients:

- The patients affected by β-TDT, when required, given the seriousness of the disease, depend for their survival and to prevent complications associated with the disease on a chronic transfusional treatment regime. Transfusion dependence is defined as at least 8 transfusions/year in the last 2 years or transfusion of a minimum 100 ml/Kg of concentrated red blood cells / year in the last 2 years.
- Patients with β-TDT followed at a Hemoglobinopathies Reference Center where it is possible to track clinical data, and in particular, data related to transfusion. At these centers, the patient also has a preliminary interview during which the available therapeutic options and the proposed procedure are discussed. The transplant Center will carry out the final interview and final assessment, and collect the informed consent form.

  It is essential that patients are followed at a Center of Reference for Hemoglobinopathies for at least 2 years and that correct registration of medical data is guaranteed, with particular attention to data concerning comorbidities, lab test results, and instrumental and transfusional data.

  Traceability of transfusional data is particularly important in order to calculate annual transfusional and iron intake requirements, to register any allo-antibodies and transfusion reactions, and also to evaluate the need for any further therapy after GT

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CH. 2 - AGE

By now it is clear that age is a risk factor for hemoglobinopathies both during conventional therapy and in a transplant setting.

Back in the '80s, the Pesaro Group had already stratified thalassemic patients aged <16 years into 3 risk groups that had a significant impact on the clinical outcome post transplant.

The statistically significant factors were hepatomegaly (<2 cm versus >2 cm from the costal margin), hepatic fibrosis (absent versus present), and chelation (regular versus irregular).

This last parameter was linked to the use of deferoxamine, the only chelating drug then available. It was important because it reflected the concept of duration and exposure to good chelation.

Surprisingly for then, but what has since become clearer to us today, the Pesaro Classification was not predictive for adult patients, probably because they had already been exposed to too long a period of iron toxicity.

The correlation between the Pesaro Classification and the new knowledge of the physiopathology of iron has now been recognized and has received fresh interpretation; in itself, it underlines the pertinence today of the observation reported almost 30 years ago. Up to now, the limited experience of registered trials investigating GT requires us to adopt a cautious approach when using this classification until fresh evidence becomes available.

Age is also considered and established by the current regulations in force. In fact, GT based on LentiGlobin (Blubird Bio) has received European Medicines Agency (EMA) approval for patients aged >12 years with β-TDT with non-β0/β0 genotype: https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo

The safety and efficacy of this therapy in children aged <12 years have still not been established.

The upper age limit is not codified as it depends on the clinical condition (comorbidities/organ damage) of the individual patients. It is, therefore, up to the physician in charge to examine the characteristics of the individual patient and evaluate the priorities to be addressed (see below.)

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Up to what age can a thalassemic patient be considered eligible for gene therapy?

Data available in the literature concern the aging processes of the medullary microenvironment in healthy subjects.

Studies carried out in elderly subjects (aged >65 years) have shown how mobilization of CD34+ cells with granulocyte-colony stimulating factor can be reduced, but always on the basis of transplant requirements.

In non-anemic elderly subjects aged between 66 and 73 years, two independent studies described a reduction in the number of peripheral CD34+ cells compared to subjects aged between 30 and 45 years.

This is associated with an increase in stem cell factor levels and a lower response to erythropoietin (EPO). Data available in the literature do not all agree on this. Furthermore, the presence of a co-morbidity such as diabetes, arterial hypertension can further alter the cell response to EPO.

Interestingly, in vitro clonal studies show that fewer BFU-E and CFU-E can be obtained in vitro in non-anemic elderly patients than in young subjects.

For the moment, patients aged >65 years do not have access to gene therapy.

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CH. 3 - ALLOGENEIC TRANSPLANTATION

In the two previous chapters we have presented the two fundamental factors that condition clinical outcome post transplant: age <14 years, according to the data of the European Hemoglobinopathies Registry, and availability of an HLA-identical family donor.

The correlation between age and clinical outcome is strictly related to organ damage resulting from long-term chronic transfusional treatment, in spite of the incredible improvements seen in treatment, chelation and supportive measures.

HLA compatibility is an extremely important tool in the transplant setting, both because it reduces the immunological complications related to antigenic disparity (graft-versus-host disease, GvHD) and because it allows less ablative and immunosuppressive conditioning regimens to be used, thus limiting the procedure-related toxicity and infection complications.

The HLA-identical family donor has been confirmed to be the donor profile that guarantees the best outcome in terms of OS and thalassemia-free survival (EFS) in the large patient cohorts; data from the European Hemoglobinopathies Registry show that patients aged <14 years with an HLA-identical family donor have OS of 91.9% and EFS of 86%.

Recent data on transplantation with alternative donors (haploidentical) in β-TDT from a single study, have shown promising results; the number of patients is, however, limited.

Age <14 years and an HLA-identical family donor promote best transplant outcome.

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CH. 4 - GENOTYPE

β-globin genotype must be registered on presentation of a report from a National Health accredited laboratory.

The HbVar database (http://globin.cse.psu.edu) can be used to define the hematologic expression (β0 o β+ forms).

At present, regulatory authorities do not request studies of alfa, delta and gamma globin genes.

However, the complete molecular globin profile could be useful in assessing the expected response to therapy, and is, therefore, strongly advised.

CH. 5 - SCIENTIFIC AND REGULATORY UP-DATE

SITE, in consideration of the continuous evolution of medical scientific knowledge, of the data presented in the literature and, in specific cases, of the revisions of the Regulatory Authorities, will up-date the document should new evidence come to light that could modify the strength of the recommendations presented here.

Should no such evidence become available, the SITE will up-date the document every 2 years

Should significant but manageable iron overload (LIC >7 mgFe/gLiver d.w.) without organ damage be considered a contraindication for gene therapy?

According to the formula recently proposed by Coates, iron-associated tissue toxicity is due to more than one factor: quantity of reactive species (non-transferrin bound iron, labile plasma iron, etc.); genetic anti-oxidant factors; environmental factors (food antioxidants, other metals such as copper, selenium, etc.); length of time exposed to the toxic effects of iron.

Recent in vitro studies have shown that accumulation of iron can influence also the medullary bone marrow microenvironment with a negative impact in terms of the quality and the quantity of the hematopoietic stem progenitor cells.

The Pesaro Experience has shown that constant monitoring of accumulation of iron represents the determining factor for transplant outcome. The Pesaro Classification, that stratifies patients on the basis of 3 independent factors (hepatomegaly, hepatic fibrosis and length of exposure time to chelating therapy), remains pertinent today because it summarizes the result of the monitoring of the accumulation of iron that the patient has been able to maintain through his or her lifetime.

In relation to this, attention should be drawn to the paragraph “Risks associated with TDT and iron overload” (see 4.4 “Special warnings and precautions for use in APENDIX I – SUMMARY OF PRODUCT CHARACTERISTICS used for GT and approved by the EMA (https://www.ema.europa.eu/en/documents/product-information/zynteglo-epar-product-information_en.pdf):

Patients with TDT experience iron overload due to chronic red blood cell (RBC) transfusions that can lead to end organ damage. HSC transplantation with myeloablative conditioning is not appropriate for patients with TDT who have evidence of severely elevated iron in the heart i.e., patients with cardiac T2 <10 msec by magnetic resonance imaging (MRI). MRI of the liver should be performed on all patients prior to myeloablative conditioning. It is recommended that patients with MRI results demonstrating liver iron content ≥15 mg/g undergo liver biopsy for further evaluation. If the liver biopsy demonstrates bridging fibrosis, cirrhosis, or active hepatitis, HSC transplantation with myeloablative conditioning is not appropriate.*

Adopting a cautious approach, we feel that more stringent criteria should be used than those indicated by the EMA. Although this is not a contraindication, it does underline the need for caution and not high priority with suspension of the indications and reassessment.

Patients with significant iron accumulation (LIC > 7mgFe/gLiver d.w) should have a “suspended indication” for GT until values return to acceptable limits (LIC<7 mgFe/gLiver); caution should be exercised and values should be monitored daily after sufficient chelation therapy has been administered

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ORGAN DAMAGE ASSESSMENT

- Cardiomyopathy
- Liver Disease
- Endocrinopathy
- Nephropathy
- Thrombophilic Status

CH. 7 – CARDIOMYOPATHY

Does cardiomyopathy condition the outcome of gene therapy β-TDT patients?

The outcome of allogeneic transplantation is strictly correlated to a good performance status, to adequate iron chelation without iron-related organ damage, and the absence of comorbidity. However, these parameters also influence the outcome of GT.

In the setting of β-TDT patients, cardiac complications and premature death for cardiomyopathy still represent a serious problem. In particular, iron-related cardiac complications represent the main cause of death and the biggest cause of morbidity. Iron-related cardiac damage is represented by cardiac insufficiency, arrhythmias, sudden death or progressive congestive heart failure.

The prevalence and predictive factors for cardiac complications in patients undergoing allogeneic transplant are not known. In trials in GT, a heart T2* MRI <10 ms and clinically significant pulmonary hypertension are conditions that exclude access to GT.

In the light of observations on restrictive myocardiopathy in adult patients with preserved Ejection Fraction (EF) and without myocardial iron overload, it is felt that these should be included in the exclusion criteria.

We consider, therefore, that the following heart conditions can exclude access to GT:

- **myocardial iron overload T2* MRI < 10 ms in the previous 6 months;**
- **pulmonary hypertension by cardiac catheterization;**
- **serious congestive heart failure (NYHA class > III);**
- **significant arrhythmia requiring therapy, as defined by EHRA guidelines;**
- **myocardial ischemia in the previous 12 months, as defined by ESC guidelines;**
- **restrictive myocardiopathy, as defined by ESC guidelines.**

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www.escardio.org

In β-TDT patients, does liver disease condition the outcome of GT?

Follow-up data on GT are lacking. It is useful, therefore, to refer to the experience of hematopoietic stem cell transplant. In 1990, Lucarelli et al. identified fibrosis and hepatomegaly as factors predictive of a negative transplant outcome and, in spite of the subsequent controversy concerning the definition of hepatomegaly, the original criteria are still to be considered valid, i.e. hepatomegaly as an expression of hepatic iron accumulation and of the duration of toxic iron exposure.

Hepatic fibrosis is a marker of exposure to iron and also to viruses. In fact, patients with liver disease, and particularly those with severe hepatic fibrosis or cirrhosis, are at higher risk of veno-occlusive disease (VOD), after myeloablative conditioning regimes, and of fatal liver failure also with reduced intensity conditioning.

The ideal thalassemic candidates for GT are, therefore, those with no or only slight hepatic fibrosis (F1 by Fibroscan® or ISHAK 0-1-(2) by liver biopsy).

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Should active or previous Hepatitis C virus (HCV) infection be considered a contraindication for GT?

Data correlating HCV infection with GT are lacking since patients positive for HCV-RNA are not enrolled on registered trials. It is useful, therefore, to refer to the experience of hematopoietic stem cell transplant.

HCV infection (HCV-RNA positivity) appears to be clinically revelant, as the hepatitis can worsen after immune reconstitution. Risk of death after reactivation is 8% and involves only the allogeneic transplant setting

HCV-positivity remains a significant risk factor for mortality after allogeneic stem cell transplantation also in subjects with normal or almost normal liver function.

This association remains a subject of debate, and is not supported by some Authors. However, others consider HCV to be an independent risk factor for post-transplant VOD.

An increase in the risk for fatal VOD in HCV-positive patients who had received cyclophosphamide and >12 Gray total body irradiation seems to be correlated to liver inflammation and fibrosis and to the components of the conditioning regimen rather than the HCV itself

Considering the availability of efficacious and safe anti-viral therapies that have given excellent results also in thalassemia patients, it does not seem justified to consider HCV-RNA-positive subjects as candidates for GT, while there are no contraindications in principle for those anti-HCV-positive patients who have eliminated the virus, either spontaneously or after anti-viral therapy, in the absence of other hepatic or extra-hepatic contraindications.

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A AISF position paper on HCV in immunocompromised patients.
DLD 2019

Should active or previous Hepatitis B virus infection be considered a contraindication for GT?

Also in this case, it is useful to refer to the experience of hematopoietic stem cell transplant.

Reactivation can be followed by normalization with seroconversion until HbsAg negativity is achieved in 25% of cases, even without anti-viral therapy, while fulminant hepatitis is observed in a small percentage of patients (3%).

In most cases, any new acute phase of hepatitis is only light and asymptomatic with a moderate and long-lasting increase in transaminase levels.

The risk of reactivation of hepatitis B in HbsAg negative and antiHBc positive subjects is around 6.5%. There are no differences between HBV-DNA positive and HBV-DNA negative subjects; among those with hematologic diseases, the risk of reactivation is higher in those treated with Rituximab.

Clinical presentation of HBV reactivation ranges from asymptomatic cases to acute liver failure and death. As stated, mortality rates are higher in those patients who do not receive anti-viral agents (approx. 30%) compared with those who do (12%); among those treated, mortality rates are lower in those treated with entecavir compared to those treated with lamivudine.

Given this, the use of anti-HBV prophylaxis is recommended in patients who are HbsAg-negative, anti-HBc-positive with hematologic diseases, independently of the basal anti-HBs and HBV DNA status.

On the other hand, the therapeutic use of 2nd-generation nucleoside analogs is strongly recommended in those subjects with active chronic HBV infection who are candidates for immunosuppressive therapy.

GT is contraindicated in patients with chronic HBV infection, as defined by EASL guidelines. GT can be considered for subjects with occult HBV infection, as defined by EASL guidelines, who accept appropriate prophylaxis, in the absence of other contraindications.

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CH. 9 – ENDOCRINOPATHY

In β-TDT patients, should the presence of one or more endocrinopathies be considered a contraindication to GT?

Correct long-term medical treatment is the essential factor for post-transplant outcome, and probably also for GT.

Endocrinopathies have been shown to be associated with higher ferritin values (in cases of late start of chelation) and cardiac overload, indicating that the presence of one or more endocrinological complications reflects an inadequate iron chelation therapy and a high iron burden in the subject involved.

The term “diabetic stem cell mobilopathy” is used to indicate scarse mobilization of the bone marrow hemopoietic stem cells to the peripheral blood in diabetic patients. This is because the diabetes radically changes the bone marrow niche and determines a net reduction in the release of hematopoietic stem cells.

In trials on GT presence of an endocrinopathy has never been cited as an exclusion criterion. However, exclusion criteria have been reported to include the statement: “Any other evidence of severe iron overload that, in the Investigator’s opinion, warrants exclusion”.

Endocrinological complications have not been shown to be revelant to post-transplant outcome.

These should, however, be assessed before transplant in order to program adequate monitoring post transplant. At this stage, a cautious approach should be adopted and insulin-dependent patients should be excluded from GT.

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In β-TDT patients, should kidney disease be considered a contraindication to GT?

In β-TDT patients, kidney damage could be related to iron overload or to chronic hypoxia due to anemia.

Here, the allogeneic transplant model can not be applied for the use of nephrotoxic immunosuppressors.

Different thresholds of chronic disease have been reported, e.g. “Kidney disease with a calculated creatinine clearance <30% normal value - Kidney disease with a baseline estimated glomerular filtration rate <70 mL/min/1.73 m2”; “Adequate renal function as evidenced by Serum creatinine < 1.5 upper limit of normal”.

Published trials on the use of GT in β-TDT patients report changes in kidney function as an exclusion criterion for trial enrollment. Kidney function must be assessed pre-transplant.

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CH. 11 - THROMBOPHILIC STATUS

In β-TDT patients, the presence of thrombotic events must be considered a contraindication for GT?

β-TDT patients present hypercoagulability, particularly evident in splenectomized patients, due to high platelet count and peripheral erythroblastosis.

In relation to peripheral stem cell mobilization and the use of G-CSF, an essential stage of GT, patients with a history of thrombotic events must be identified and their thrombophilic status assessed.

Published trials on the use of GT in β-TDT patients confirm thrombotic events to be an exclusion criterion for enrollment as does hypersplenism that could have a negative impact on grafting.

Assessment of pro-thrombotic status emerges as an essential factor in order to promote good transplant outcome.

Patients with "Low risk thrombophilic screen and negative history of significant previous thrombotic events" are considered eligible for enrollment while those with "A white blood cell (WBC) count <3 × 109/L, and / or platelet count <100 × 109/L if not due to hypersplenism - Uncorrected bleeding disorder" are not".

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CH. 12 – SUMMARY

It is the opinion of the SITE Group of Experts that patients with β-TDT who could represent possible candidates for GT with the only product currently available that is approved by the EMA (EMA/CHMP/166977/2019) (Zynteglo®) must satisfy the following characteristics:

High priority patients:

- patients followed by Specialized Hemoglobinopathies Centers;
- β-TDT patients aged >12<65 years;
- genotype non-β0/β0;
- patients eligible for allogeneic transplant with no HLA-identical family donor;
- no significant iron overload;
- no organ damage;
- be registered in a qualified transplant center with experience in HSCT and in treatment of patients with β-TDT;
- good compliance to treatment.

Excluded patients:

- patients not followed by Specialized Hemoglobinopathies Centers;
- aged <12>65 years;
- uncontrolled iron overload;
- chronic organ damage, hepatopathy, insulin-dependent diabetes, nephropathy, positive thrombophilic status.

Assessable patients undergoing ongoing changes to therapy:

- patients followed by Specialized Hemoglobinopathies Centers;
- β-TDT patients aged >12<65 years;
- genotype non-β0/β0;
- patients eligible for allogeneic transplant with no family HLA-identical donor;
- iron overload: LIC >7mgFe/gLiver d.w – cardiac MRI T2* < 10 ms in the previous 6 months;
- non-insulin dependent diabetes;
- slight and/or reversible cardiopathy;
- HCV-RNA positive;
- good compliance to treatment.