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Progress in Hematopoietic Stem Cell Transplantation

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1. Introduction

Transplantation of autologous or allogeneic hematopoietic stem cells is a method currently used to treat many malignant and nonmalignant hematological diseases. The indications, methods, goals of therapy have evolved since the introduction of transplantation to the clinical practice. Progress that has been achieved allowed for the improvement of results. Thanks to the availability of various conditioning regimens, various hematopoietic cells sources as well as variable possibilities of anti-GvHD prophylaxis the individualization of the transplantation procedure has been more and more widely used in the recent years. This chapter summarizes current clinical practices and presents major clinical problems that have to be optimally managed in order to improve the outcomes of transplantation.

2. Autologous hematopoietic stem cells transplantation

Autologous peripheral hematopoietic stem cells transplantation (auto-HSCT) was for the first time performed at Hammersmith Hospital in London in 1981 to treat the patient in accelerated phase of CML. Although auto-HSCT does not play any role in the treatment of CML nowadays, indications for this valuable therapeutic method have evolved for many years. In acute leukemia auto-HSCT should be recommended only in the context of clinical studies. Auto-HSCT after myeloablative chemotherapy or radiotherapy has originally been developed as an alternative to allogeneic hematopoietic stem cell transplantation for patients with AML with no suitable donor. Several randomized studies in patients with AML

in first complete remission (CR1) subsequently suggested reduced relapse rates after auto-HSCT [1]. Auto-HSCT is also widely used to consolidate first remission in AML. The novel molecular and cytogenetic stratification methods may allow the identification of AML entities which could benefit from autografting. The overall survival of patients receiving auto-HSCT in ALL in first remission is around 40%. The high-dose therapy followed by auto-HSCT can be an alternative treatment in patients in whom allo-HSCT is precluded.

The results of a large European study showed that auto-HSCT can be recommended in patients with good-risk cytogenetic characteristics of myelodysplastic syndrome [2]. Auto-HSCT can be recommended as post-remission therapy to reduce the risk of relapse. The longer remission was observed in patients who undergo auto-HSCT.

In myeloproliferative disorders auto-HSCT can induce responses in patients with primary myelofibrosis, but this procedure cannot be recommended out of clinical protocols.

In chronic lymphocytic leukemia auto-HSCT can be considered for patients with poor-risk disease in complete or good partial remission able to withstand high-dose therapy, but it should be performed preferably in the context of clinical protocols.

Auto-HSCT is the standard therapy for patients with Hodgkin's lymphoma (HL) in first chemosensitive relapse or second complete remission as shown by two prospective randomized clinical trials [3,4]. There is no indication for auto-HSCT in first remission, even in patients with poor prognosis at diagnosis [5,6]. Patients refractory to first-line therapy but sensitive to salvage therapy might benefit from auto-HSCT [7]. Auto-HCT might be considered as a part of a clinical protocol for patients with resistant Hodgkin's lymphoma, as an initial debulking therapy to be followed by an allo-HSCT as consolidation therapy [8].

In many non-Hodgkin's lymphomas auto-HSCT is a standard therapy. In diffuse large B-cell lymphoma (DLBCL) auto-HSCT is a standard therapy for patients with chemosensitive relapse [9]. The role of auto-HSCT is being re-evaluated with the advance of monoclonal antibodies and use of chemo-immunotherapy as first-line treatment. Auto-HSCT remains also the standard approach for early relapsing patients with follicular lymphoma (FL) [10]. In both DLBCL and FL, auto-HSCT does not provide any clinical benefit in patients with refractory disease. Otherwise, most patients with mantle cell lymphoma are being offered an early intensification with an auto-HSCT, owing it to the inherent poor prognosis of the disease. The retrospective analysis indicates that the results of auto-HSCT performed beyond the first remission are inferior [11]. Few studies showed an improved survival in patients with T-cell non-Hodgkin's lymphoma (NHL) who received auto-HSCT as a first line treatment, compared to those who did not.

Patients with multiple myeloma form a large group of patients being transplanted. Auto-HSCT is clearly indicated for patients <70 years of age with satisfactory general health and fitness who respond to the first-line treatment. Although new agents change the place of auto-HSCT in MM, this procedure still has an established position in treatment. Best results are observed in patients achieving good response before the auto-HSCT, but some non-responding patients also may benefit from this approach. Double auto-HSCT (or tandem auto-HSCT) has been shown to be superior to consolidation and maintenance with agents such as

thalidomide in patients not achieving the remission or a very good partial response after the first transplant [12].

Auto-HSCT constitutes an important treatment option for patients with solid tumors. Selected subgroups of oncological patients may benefit from high-dose chemotherapy supported by auto-HSCT. High-dose chemotherapy for refractory germ cell tumors is considered a standard therapy. Conditioning regimen in this case incorporates carboplatin and etoposide.

Auto-HSCT after conditioning regimen aimed to increase the immunosuppression is being considered in clinical protocols for selected patients with severe multiple sclerosis [13], rheumatoid arthritis [14], systemic lupus erythematosus [15], systemic sclerosis [16], immune cytopenias and Crohn's disease [17]. Auto-HSCT for other autoimmune disorders is being considered on a developmental basis. Steroid dependency with Cushing threshold and skeletal damage could be an indication.

3. Allogeneic hematopoietic stem cell transplantation

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) constitutes a standard treatment of hematological malignant and nonmalignant disorders. The possibility of finding a donor has been increased by use of unrelated donors, with similar results of transplantation when compared to results of sibling donor transplants. The use of peripheral blood stem cells, instead of bone marrow, results in faster engraftment, but also in the increased risk of chronic GvHD (Graft versus Host Disease). Reduced-intensity conditioning is used instead of high-dose myeloablative conditioning for older patients and those with comorbidities. Disease relapse is a major problem and thus it should be detected as early as possible, at the stage of the minimal residual disease or recurrent recipient chimerism and managed by immunotherapy with donor lymphocyte infusions. Novel diagnostic tools and anti-microbial drugs have reduced the morbidity and mortality from infections.

Allogeneic hematopoietic stem cell transplantation connected with application of high-dose chemo- and radiotherapy was first carried out by Thomas et al. in 1957 to treat leukemia patient in advanced stage [18]. The concept of treatment at that time was based on the previous observations conducted during the second world war, referring to destructive activity of radiation on the function of bone marrow, as well as further research conducted in the 1950's, which showed that it was possible to avoid irreversible pancytopenia thanks to the bone marrow cells transplantation in the irradiated animals. The discovery of Human Leucocyte Antigen (HLA) enabled to match appropriately the donor and the recipient, what contributed to the significant increase in overall survival after transplantation which has been observed since 1968 [19]. The improvement of the results was undoubtedly also influenced by other factors: performing the transplantation in the optimal phase- remission of the disease, GvHD prevention, the improvement of adjunctive treatment. Nowadays more than 25.000 allo-HSCTs are being performed each year.

The main indication for allo-HSCT is acute myeloblastic leukemia (AML) and acute lymphoblastic leukemia (ALL). In high risk ALL and AML, when favorable prognostic genetic

changes are lacking, the allo-HSCT is recommended in the first remission of the disease. The transplantation in more advanced stages of the disease leads to the higher relapse rate, as well as to the increased incidence of transplantation complications.

Despite the introduction of tyrosine kinase inhibitors (TKIs) into the treatment of chronic myeloid leukemia (CML) over ten years ago, allo-HSCT still remains the only way of treatment capable to provide the complete recovery. The standard indication for allo-HSCT is resistance to TKIs treatment, especially in young patients. Other indications for allo-HSCT are myelodysplastic syndrome, high-risk chronic lymphocytic leukemia, selected patients with high-risk lymphoma, patients with myelofibrosis and other myeloproliferative neoplasms of unfavorable prognosis. The results of multiple myeloma treatment with the use of allo-HSCT are encouraging. Allo-HSCT with the reduced conditioning regimen after previous auto-HSCT constitutes an interesting alternative in patients with multiple myeloma patients, who undergo single or tandem autologous transplantation [20].

Allo-HSCT is also the standard treatment in nonmalignant diseases of hematopoietic system such as severe aplastic anemia (SAA), paroxysmal nocturnal hemoglobinuria (PNH) and hemoglobinopathies. In some cases of inborn metabolic defects, allogeneic transplantation of donor's cells can restore the production of the deficient or lacking enzyme and eliminate the disease [21].

4. Hematopoietic stem cell donors

The optimal donors are siblings possessing both haplotypes identical with the recipient. The syngeneic transplantation, i.e. from monozygotic twins, is the safest from the immunological point of view, however it is connected with the increased risk of the relapse of the disease resulting from the lack of immunological interaction between the donor cells and the recipient cells [22].

Probability of possessing matched sibling donor is defined by the formula: $1 - (0.75)^n$, where n indicates the number of siblings. The observed decrease in the number of newly born children causes problems in finding matched family donors for many patients. In rare cases with no matched sibling donor, matching donor could be found among other members of the family. In the vast majority of patients without matched sibling donor, transplantation from unrelated donor is the most frequently chosen option. The number of such transplantations has increased considerably in the last 20 years [23]. It has been made possible thanks to dynamic development of bone marrow donors' registries, whose number of potential donors exceeded 20 million in the current year 2012. Alternatively, for those patients who are unlikely to find a matched donor, partial incompatibility could be accepted.

The most desirable model of the donors' registry organization is the development of national ones which, for many reasons (safety of donors, clearness of procedures and financial reasons), according to WMDA's (World Marrow Donors Association) recommendations should control and supervise the recruitment of the donors within the country. The chance to find

the matched donor depends on the frequency of occurrence of HLA-haplotypes in the whole population and the race of recipient – most donors recruited by registries worldwide belong to Caucasian race. The efforts are being made, especially in the USA, aiming to recruit higher number of donors of other races.

Phenotypic HLA-matching involving the testing of HLA-antigens by means of specific sera has been replaced by more precise molecular testing enabling the precise identification of HLA allelic determinants.

The question of accepting a mismatched donor for a patient, who didn't find a fully matched donor has not been finally solved. With the increasing number of observations there are recommendations concerning optimal matching not only in HLA-A, B and DR, but also in C, DQ and even DP. Many centers aim to transplant patients only from donors fully matched in 10/10 alleles of HLA-A, B, C, DR and DQ. The improved methods of typing enabling more precise molecular donor matching has improved the results of allo-HSCT from unrelated donors, which are now similar to those of allo-HSCT from siblings [24]. As the allo-HSCT from an unrelated donor has to be preceded by often time-consuming search for a donor, it is important to plan the transplantation carefully in advance.

5. The sources of hematopoietic stem cells

The choice of the cells source depends of diagnosis and the type of conditioning treatment applied. Collection of bone marrow is preferred in nonmalignant diseases in order to avoid chronic GvHD. Transplantation of hematopoietic cells from peripheral blood is preferred when reduced intensity conditioning regimen is used, with regard to the fact that transplantation of larger number of hematopoietic cells is able to break the resistance of the recipient and to result in the engraftment.

The bone marrow aspirated in general anesthesia from iliac spine was for many years the main source of cells for transplantation. Except of hematopoietic cells, the bone marrow also consists of multipotential mesenchymal cells which, although are not hematopoietic cells, have a potential to differentiate in vitro and in vivo into various mesenchymal tissues, such as bone, cartilage, fat tissue, tendons and bone matrix. Mesenchymal stem cells can reduce the alloreactivity, they inhibit lymphocytes T proliferation and act immunosuppressively, what has been implemented in the form of unrelated or haploidentical mesenchymal cells infusion into the treatment of acute GvHD.

During the 1990's the cells collected in apheresis from peripheral blood after their previous stimulation with granulocytic stimulating factor (G-CSF) completely superseded the bone marrow aspiration in autologous transplantations. In the beginning of 21st century, the similar trend occurred also in allo-HSCT. The apheresis of cells from peripheral blood usually results in collection of higher number of nucleated cells, CD34+ cells, lymphocytes CD3+ and NK cells when compared with cells aspiration from the bone marrow; it enables faster regeneration of granulocytes and platelets. It translates into the smaller risk of infections and smaller demand for transfusions of blood derivatives.

In the beginning allo-HSCT in the form of PBSCT (Peripheral Blood Stem Cells Transplantation) was applied only in sibling transplantations due to the anxiety of acute GvHD occurrence, however, the frequency of GvHD is similar to the one after bone marrow transplantation, despite greater number of T-lymphocytes in the transplantation material collected from peripheral blood, as it was shown in the number of studies. Thus allo-PBSCT has been successfully applied also in allo-HSCT from unrelated donors. However, the frequency of chronic GvHD is higher, and thus allo-PBSCT is applied seldom in patients with nonmalignant disease, who do not benefit from Graft versus Leukemia (GvL) effect, which is usually connected with chronic GvHD [25].

The important source of hematopoietic stem cells for allo-HSCT is a cord blood (CB), usually intended to be discarded. In many countries there are banks of frozen CB units where there are over 0,5 million units ready to be transplanted. The advantage of applying CB cells is their immediate availability and a reduced risk of GvHD, related to a relative shortage of mature T-lymphocytes in the CB. Therefore the higher level of HLA-mismatching between the donor and the recipient is more acceptable in CB transplantation than in traditional transplantations. The unfavorable factors are a more frequent occurrence of graft failure and a slower regeneration responsible for higher risk of infections. The number of necessary nucleated cells and CD34+ cells calculated per kilogram of the recipient's body mass is lower by about one logarithm when compared to the bone marrow. A number of studies showed the importance of sufficient number of cord blood nucleated cells, for this reason it is recommended to transplant more than 2×10^7 nucleated cells per kilogram of recipient's body mass. It constitutes limitation in CB application in adults due to the small volume of cord blood and small total number of cells. Simultaneous transplantation of two CB units is successfully applied to solve this problem [26,27]. In vitro cells expansion to increase the number of CB cells has not been widely used. Because of the limited, usually small number of cord blood cells, it is most often applied as the source of cells for transplantation in children.

6. Preparative treatment before transplantation

The preparative treatment before transplantation (or conditioning regimen) aims to eradicate the remains of the disease and to make immunological system of recipient weaker in order to enable the acceptance of the graft by the recipient. The preparative treatment is connected with toxicities which turned out to be impossible to eliminate so far.

The choice of conditioning treatment depends of the patient's age, the main disease and co-existing diseases. Myeloablative conditioning regimens are characterized by strong cytotoxicity as well as strong immunosuppressive potential, while reduced intensity conditioning regimens differ in cytotoxic activity and immunosuppressive potential. They are chosen depending on the main disease and evaluation of the risk of graft failure.

The combination of radiotherapy (TBI- total body irradiation- at total dose of 12 Gy, delivered in fractions) and cyclophosphamide (Cy, at total dose of 120 mg/kg administered within 2 days) has been used for over 40 years for conditioning [28]. TBI treatment is

recommended as a standard in ALL. In order to avoid potential TBI consequences, such as bronchiolitis obliterans, cataract, secondary malignancy, endocrinological disorders, inhibition of the growing process in children, TBI in AML and MDS has been replaced by busulfan given at 16 mg/kg dose within 4 consecutive days before Cy [29]. The BuCy treatment has higher risk of SOS (sinusoidal obstruction syndrome), hemorrhagic cystitis and chronic GvHD. The high serum concentration of Bu (Busulfan) occurring during its oral treatment has influenced considerably its toxic complications. It is difficult to avoid it because of various degree of absorption from digestive tract. Thus the intravenous use of busulfan is more favorable. The reduction of SOS incidence and decrease of transplant related mortality (TRM) after intravenous use of Bu has been reported [30]. In order to further limit the toxicity, treosulfan is used instead of Bu in modern treatment programs nowadays, and additional immunosuppressive effect is obtained by parallel application of purine analogue, e.g. fludarabine.

The standard preparative treatment applied in SAA comprises of Cy 200 mg/kg and antithymocyte globulin (ATG).

Although the intensive conditioning treatment decreases the risk of relapse after transplantation, it does not prolong the overall survival because greater toxicity leads to increased transplant related mortality [31].

The concept of so-called RIC (reduced intensity conditioning) incorporates the advantage of anti-leukemic effect of donor T-lymphocytes while cytotoxic effect of conditioning regimen is decreased. The main result of RIC treatment is immunosuppressive therapy aiming to enable the acceptance of the transplant by braking the immunological defence of the recipient. The anti-leukemic effect can be escalated after transplantation by means of DLI (Donor Lymphocyte Infusion), whenever it is required. DLI was first used with success in CML patients, in whom the disease relapsed after conventional allo-HSCT [32]. Since then it has been used in many other diseases, including many clonal diseases of hematopoietic system, most often lymphomas and chronic lymphocytic leukemia (CLL). RIC treatment has lower toxicity when compared to conventional conditioning treatment, thus it is suitable for transplantation in older patients and in patients with coexisting diseases in whom the application of myeloablative treatment is contraindicated. RIC treatment consists most often of purine analogue. The example of RIC treatment reduced to the minimum, after which graft occurs, is the combination of TBI dose 2Gy with fludarabine. Other exemplary RIC protocols are the combination of fludarabine with Bu at dose 8 mg/kg and ATG with Cy or with melphalan. The important element of RIC treatment is the use of immunosuppressive therapy after transplantation e.g. cyclosporine A and mycophenolate mofetil. The reduced intensity of conditioning enables the immunocompetent recipient cells to survive until the moment of transplantation, what leads to the higher risk of graft failure or incomplete graft. In some centers transplantation with RIC are performed in ambulatory, however patients often require further hospitalization due to infections or GvHD [33].

Allo-HSCT with use of RIC can be applied when autologous transplantation is ineffective. Other possibility is to apply the tandem transplantation: at first autologous one and then the allogeneic one, with use of RIC in order to reduce the TRM by separation of high-dosed cy-

totoxic treatment from immunotherapy related to allogeneic HSCT, which has been applied for the first time in patients with multiple myeloma (MM).

7. Adjunctive treatment

During the phase of pancytopenia after myeloablative conditioning patients are usually susceptible to infections and thus they have to stay in a sterile environment, e.g. in HEPA-filtered rooms with reversed isolation. They routinely receive preventive treatment against bacteria, viruses, fungi. Moreover, the substitution treatment is applied with the use of irradiated, CMV-negative red blood cells and single donor platelets concentrates. Analgetic drugs and parenteral nutrition are applied when needed. Ursodeoxycholic acid is used in order to avoid hepatic complications. G-CSF is applied to accelerate the regeneration of granulocytes, however it can delay the recovery of platelets and can increase the risk of GvHD. Erythropoietin accelerates the recovery of red blood cells system and thus it reduces the need for transfusions, but it increases the cost of the transplant procedure and it is not used on a regular basis.

8. Post-transplant complications

8.1. Graft versus host disease

Acute and chronic graft versus host disease are the main complications of allo-HSCT. In pathophysiology of acute and chronic GvHD, T-lymphocytes of the donor recognize HLA-molecules of the recipient presented by the antigen presenting cells. It results in the release of interleukin-2 and activation of cytotoxic T-lymphocytes, NK-cells and macrophages. The main targets of the attack are skin, gut and liver. The most important risk factor is the HLA-incompatibility between the donor and the recipient, but also minor histocompatibility antigens are responsible for the risk of GvHD, especially HY mismatch in case when the donor is female and the recipient is male [34]. Chronic GvHD occurs most often from 100 days to one year after allo-HSCT. It resembles autoimmune diseases, e.g. systemic sclerosis and Sjögren syndrome. Symptoms such as lichen and sclerodermic skin changes, mucositis, xerostomia, keratoconjunctivitis sicca, stricture of esophagus and vagina, cholestatic liver failure, bronchiolitis obliterans and myositis also occur. Cachexia, immunological deficiency, additionally increasing the risk of infections especially caused by gram-plus bacteria can be also observed. The initial stage of chronic GvHD is usually more progressive when it is preceded by the acute form of the disease. It can also occur after nonsymptomatic (quiescent) period or de-novo, without any preceding symptoms of acute GvHD. The chronic progressive GvHD has the worst prognosis.

In order to decrease the risk of GvHD a preventive immunosuppression, usually with the use of cyclosporine A (CsA) and methotrexate is applied. The removal of T-lymphocytes from the transplanted cells (T-depletion) constitutes the effective form of prevention, how-

ever, it is connected with the higher risk of the graft failure and relapse of the disease. In cord blood transplantations, instead of methotrexate which prolongs the regeneration period, prednisolon is used. New immunosuppressive protocols include calcineurin-inhibitors other than cyclosporine A – tacrolimus, macrolid immunosuppressant– sirolimus and mycophenolan mofetil. The administration of ATG before transplantation is an important immunosuppressive element used in allo-HSCT from unrelated donors. As the effective serum concentration of ATG is maintained for many weeks after infusion, it effects not only T-lymphocytes of the recipient but also those of the donor [35]. The increased risk of infections is an undesirable side effect of ATG.

The type of GvHD prevention depends of the diagnosis, the type of conditioning treatment and the applied cell source. The GvHD prevention should be more effective in nonmalignant disease and less intensive when lower number of cells have been transplanted.

When symptoms of acute GvHD develop despite its prophylaxis, methylprednisolone at the dose of 2-5 mg per kilogram of body weight per day is used on the standard basis, usually effectively. In case of steroid resistance the risk of failure is high. The second line treatment consists of ATG, anti-IL-2 antibodies, anti-IL-2 receptor antibodies and antibodies against TNF-alpha. Photosensitizing psolarens and ultraviolet radiation in a form of extracorporeal photopheresis and transplantation of mesenchymal stem cells can be also applied, but are not everywhere available. Mesenchymal stem cells have strong immunosuppressive effect, they can be obtained from the primitive connective tissue of the umbilical cord, called the Wharton's jelly, and they do not require any matching due to low levels of HLA-ABC and lack of HLA-DR antigens.

The treatment of chronic GvHD consists of CsA and steroids. In patients not responding to the treatment tacrolimus, thalidomide, mycophenolan mofetil, sirolimus and irradiation of lymphatic system with dose of 1 Gy can be applied.

8.2. Infections

Immunological reconstitution is of a primary importance to avoid infections after allo-HSCT. The highest risk of the infection occurs in patients with GvHD, but also in the remaining patients with no GvHD it is 20 times higher than in the whole population. From 20% up to 50% of patients still require immunosuppressive treatment after 3 years from allo-HSCT, what considerably increases the risk of infectious complications in this group of patients [36].

Normal endogenous Gram-negative flora from the gastrointestinal tract and exogenous catheter-related Gram-positive bacteria constitute the most frequent cause of infections in the early stage after allo-HSCT. In this stage fungal infections are also the problem, especially other than *Candida albicans*, which are usually recognized with the delay. Although mycological diagnosis based on PCR method is available, it has not been introduced into practice yet. Galactomannan testing and detection of specific fungal antigens in the blood are sometimes helpful. In the treatment we already administer not only conventional amphotericine B with considerable side effects, but also its lipid-based preparations (Abelcet,

AmBisome, Amphocil) being better tolerated, but unfortunately expensive. New antifungal drugs such as echinocandins (caspofungin, anidulafungin, micafungin) and newer azole drugs (voriconazole, posaconazole) are also currently available.

After resolution of pancytopenia cytomegalovirus infection is a most frequent problem. Thanks to a modern diagnostic approach based on early CMV antigen detection by means of PCR methods, CMV reactivation can be detected and cured before CMV disease is developed. The most common cause of CMV infection is latent virus reactivation in CMV-seropositive patient or CMV-transmission from a seropositive donor to a seronegative recipient. Therefore the optimal situation is when the serological status of the donor and the recipient is identical. The antiviral prevention includes the substitution of blood products from CMV-seronegative donors, transfusion of immunoglobulines and administration of antiviral drugs such as gancyclovir, foscavir, cydofovir and oral valgancyclovir. Polyoma- BK virus and adenovirus are common causes of dysuria, urinary tract infections and haemorrhagic cystitis in immunocompromised patients. Epstein-Barr virus can cause post-transplant lymphoproliferative disease (PTLD). The risk factors are the use of anti-thymocyte globulin and transplantation from unrelated donors. Monitoring of EBV-viremia by means of PCR methods enables to start the treatment early – to reduce the immunosuppression and to use rituximab (anti-CD20 antibody) and donor lymphocyte infusion (DLI).

8.3. Relapse of the disease

Having better adjunctive treatment and more effective GvHD prevention, the relapse of basic disease constitutes the main cause of allo-HSCT failure. The risk of the relapse depends on the type of the disease, its stage at the moment of transplantation and the GvHD prevention applied (the more effective immunosuppression, the higher risk of the relapse). The longest survival time is observed in patients with moderate acute or limited chronic GvHD, because of the lowest risk of the relapse.

Although the relapse after allo-HSCT can be treated by means by DLI, good prognosis refers usually to the patients with CML. In acute leukemia relapsing after allo-HSCT the temporary response can be also achieved, but it is usually not stable.

Patients with molecular CML relapse, i.e. with reappearance of bcr/abl transcript in PCR tests, have better prognosis than those with hematological relapse. The prognosis in patients with more advanced stages of CML- relapse, acceleration phase or blastic transformation- is much worse. The relapse should be detected as soon as possible, when there is still a chance for effective immunotherapy after allo-HSCT.

The alternative to specific disease markers determination is post-transplant chimerism testing. The PCR short tandem repeats (STR) method is used. The goal of allo-HSCT is to obtain the full donor's chimerism. Detection of returning or increasing recipient's chimerism can be a sign of the relapse of the disease, similarly to the re-occurrence of minimal residual disease [37]. In such case it is recommended to use adoptive immunotherapy by reduction of immunosuppressive treatment and DLI application. The chimerism testing is important also for

prediction and analysis of the graft failure and GvHD risks. GvHD and pancytopenia can develop as the side effects of DLI. The use of T-lymphocytes in escalating doses is equally effective as high DLI dose, but it decreases the risk of GvHD [38].

9. New indications for transplantation of hematopoietic stem cells

Allo-HSCT with subsequent immunotherapy can be applied in patients with metastatic solid tumors. The presence of graft versus tumor effect has been shown in kidney cancer, colon adenoma, metastatic breast, ovarian, prostate and pancreas cancers. RIC treatment has been used in these conditions in order to reduce TRM while enabling to achieve the response, which was complete in some cases [39]. The presence of fewer than 3 metastases and Karnofsky scale ≥ 70 constitutes beneficial prognostic factors [40]. The survival is longer in patients who develop chronic GvHD after DLI.

Allo-HSCT is currently tested in animal models and in experimental clinical applications. Hematopoietic stem cells are characterized by plasticity, which means that they can form not only blood cells. Hematopoietic stem cells can be forced to transform into the cells of various tissues such as heart muscle, bone or blood vessels in suitable conditions [41]. The science dealing with plasticity of stem cells is just developing, but it arises hope for revolution in the way of thinking about transplantation and organ regeneration.

10. Conclusion

Allo-HSCT procedure has transformed from the experimental method of treatment of leukemia in its final stage into routine procedure applied in patients with various hematological diseases. The ability to collect and to transplant hematopoietic cells makes it possible to cure many patients with malignant and nonmalignant diseases incurable with other methods. Thanks to development of unrelated donor registries the treatment with allo-HSCT can be currently offered not only to the patients having HLA-matched sibling donor but to almost every patient in need. The observed increase of transplantations of peripheral hematopoietic stem cells results from observed faster regeneration of hematopoietic system than after bone marrow transplantation and from beneficial GvL effect in clonal diseases, although it coincides with more frequent occurrence of GvHD.

The patients in the older age group and those with comorbidities can be treated with allo-HSCT after preparation with RIC. Still, the main problem is the relapse of the disease, however when it is detected early basing on chimerism analysis and minimal residual disease evaluation, it can be successfully treated with immunological intervention with DLI. Recent and current studies indicate that hematopoietic stem cells will be used for new clinical applications in the near future.

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References

- [1] Woods WG, Neudorf S, Gold S, Sanders J, Buckley JD, Barnard DR, Dusenbery K, DeSwarte J, Arthur DC, Lange BJ, Kohn N; Children's Cancer Group. A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid leukemia in remission. *Blood*. 2001; 97(1):56-62.
- [2] Oosterveld M, Suciu S, Verhoef G, Labar B, Belhabri A, Aul C, Selleslag D, Ferrant A, Wijermans P, Mandelli F, Amadori S, Jehn U, Muus P, Zittoun R, Hess U, Anak O, Beeldens F, Willemze R, de Witte T. The presence of an HLA-identical sibling donor has no impact on outcome of patients with high-risk MDS or secondary AML (sAML) treated with intensive chemotherapy followed by transplantation: results of a prospective study of the EORTC, EBMT, SAKK and GIMEMA Leukemia Groups (EORTC study 06921). *Leukemia*. 2003; 17(5):859-68.
- [3] Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, Boissevain F, Zschaber R, Müller P, Kirchner H, Lohri A, Decker S, Koch B, Hasenclever D, Goldstone AH, Diehl V; German Hodgkin's Lymphoma Study Group; Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002; 359(9323):2065-71.
- [4] Carella AM, Bellei M, Brice P, Gisselbrecht C, Visani G, Colombat P, Fabbiano F, Donelli A, Luminari S, Feugier P, Browett P, Hagberg H, Federico M. High-dose therapy and autologous stem cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy: long-term results. *Haematologica*. 2009; 94(1):146-8.
- [5] Federico M, Bellei M, Brice P, Brugiatelli M, Nagler A, Gisselbrecht C, Moretti L, Colombat P, Luminari S, Fabbiano F, Di Renzo N, Goldstone A, Carella AM; EBMT/GISL/ANZLG/SFGM/GELA Intergroup HD01 Trial. High-dose therapy and autologous stem-cell transplantation versus conventional therapy for patients with ad-

vanced Hodgkin's lymphoma responding to front-line therapy. *J Clin Oncol*. 2003; 21(12):2320-5.

- [6] Proctor SJ, Mackie M, Dawson A, White J, Prescott RJ, Lucraft HL, Angus B, Jackson GH, Lennard AL, Hepplestone A, Taylor PR. A population-based study of intensive multi-agent chemotherapy with or without autotransplant for the highest risk Hodgkin's disease patients identified by the Scotland and Newcastle Lymphoma Group (SNLG) prognostic index. A Scotland and Newcastle Lymphoma Group study (SNLG HD III). *Eur J Cancer*. 2002; 38(6):795-806.
- [7] Moskowitz CH, Kewalramani T, Nimer SD, Gonzalez M, Zelenetz AD, Yahalom J. Effectiveness of high dose chemoradiotherapy and autologous stem cell transplantation for patients with biopsy-proven primary refractory Hodgkin's disease. *Br J Haematol*. 2004; 124(5):645-52.
- [8] Carella AM, Cavaliere M, Lerma E, Ferrara R, Tedeschi L, Romanelli A, Vinci M, Pionotti G, Lambelet P, Loni C, Verdiani S, De Stefano F, Valbonesi M, Corsetti MT. Autografting followed by nonmyeloablative immunosuppressive chemotherapy and allogeneic peripheral-blood hematopoietic stem-cell transplantation as treatment of resistant Hodgkin's disease and non-Hodgkin's lymphoma. *J Clin Oncol*. 2000; 18(23):3918-24.
- [9] Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, Sonneveld P, Gisselbrecht C, Cahn JY, Harousseau JL, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995; 333(23):1540-5.
- [10] Schouten HC, Qian W, Kvaloy S, Porcellini A, Hagberg H, Johnson HE, Doorduijn JK, Sydes MR, Kvalheim G. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol*. 2003; 21(21):3918-27.
- [11] Ljungman P, Bregni M, Brune M, Cornelissen J, de Witte T, Dini G, Einsele H, Gaspar HB, Gratwohl A, Passweg J, Peters C, Rocha V, Saccardi R, Schouten H, Sureda A, Tichelli A, Velardi A, Niederwieser D; European Group for Blood and Marrow Transplantation. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe 2009. *Bone Marrow Transplant*. 2010; 45(2):219-34.
- [12] Rosiñol L, Pérez-Simón JA, Sureda A, de la Rubia J, de Arriba F, Lahuerta JJ, González JD, Díaz-Mediavilla J, Hernández B, García-Frade J, Carrera D, León A, Hernández M, Abellán PF, Bergua JM, San Miguel J, Bladé J; Programa para el Estudio y la Terapéutica de las Hemopatías Malignas y Grupo Español de Mieloma (PETHEMA/GEM). A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood*. 2008 ; 112(9):3591-3.

- [13] Saccardi R, Freedman MS, Sormani MP, Atkins H, Farge D, Griffith LM, Kraft G, Mancardi GL, Nash R, Pasquini M, Martin R, Muraro PA; European Blood and Marrow Transplantation Group; Center for International Blood and Marrow Research; HSCT in MS International Study Group. A prospective, randomized, controlled trial of autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: a position paper. *Mult Scler*. 2012; 18(6):825-34.
- [14] Snowden JA, Kapoor S, Wilson AG. Stem cell transplantation in rheumatoid arthritis. *Autoimmunity*. 2008; 41(8): 625-31.
- [15] Marmont AM, Burt RK. Hematopoietic stem cell transplantation for systemic lupus erythematosus, the antiphospholipid syndrome and bullous skin diseases. *Autoimmunity*. 2008; 41(8):639-47.
- [16] Farge D, Nash R, Laar JM. Autologous stem cell transplantation for systemic sclerosis. *Autoimmunity*. 2008; 41(8):616-24.
- [17] Cassinotti A, Annaloro C, Ardizzone S, Onida F, Della Volpe A, Clerici M, Usardi P, Greco S, Maconi G, Porro GB, Deliliers GL. Autologous haematopoietic stem cell transplantation without CD34+ cell selection in refractory Crohn's disease. *Gut*. 2008; 57(2):211-7.
- [18] Thomas ED, Lochte HL Jr, Lu Wc, Ferrebbe JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N Engl J Med*. 1957;257(11): 491-6.
- [19] Bach FH, Albertini RJ, Joo P, Anderson JL, Bortin MM. Bone-marrow transplantation in a patient with the Wiskott-Aldrich syndrome. *Lancet*. 1968;2(7583):1364-6.
- [20] Rotta M, Storer BE, Sahebi F, Shizuru JA, Bruno B, Lange T, Agura ED, McSweeney PA, Pulsipher MA, Hari P, Maziarz RT, Chauncey TR, Appelbaum FR, Sorrow ML, Bensinger W, Sandmaier BM, Storb RF, Maloney DG. Long-term outcome of patients with multiple myeloma after autologous hematopoietic cell transplantation and non-myeloablative allografting. *Blood*. 2009; 113(14):3383-91.
- [21] Peters C, Steward CG; National Marrow Donor Program; International Bone Marrow Transplant Registry; Working Party on Inborn Errors, European Bone Marrow Transplant Group. Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines. *Bone Marrow Transplant*. 2003; 31(4): 229-39.
- [22] Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, Rimm AA, Ringdén O, Rozman C, Speck B, et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood*. 1990; 75(3):555-62.
- [23] Hows J, Bradley BA, Gore S, Downie T, Howard M, Gluckman E. Prospective evaluation of unrelated donor bone marrow transplantation. The International Marrow Unrelated Search and Transplant (IMUST) Study. *Bone Marrow Transplant*. 1993; 12(4): 371-80.

- [24] Ringdén O, Schaffer M, Le Blanc K, Persson U, Hauzenberger D, Abedi MR, Olerup O, Ljungman P, Remberger M. Which donor should be chosen for hematopoietic stem cell transplantation among unrelated HLA-A, -B, and -DRB1 genomically identical volunteers? *Biol Blood Marrow Transplant*. 2004; 10(2):128-34.
- [25] Bensinger WI, Storb R. Allogeneic peripheral blood stem cell transplantation. *Rev Clin Exp Hematol*. 2001; 5(2):67-86.
- [26] de Lima M, Shpall E. Strategies for widening the use of cord blood in hematopoietic stem cell transplantation. *Haematologica*. 2006; 91(5):584-7.
- [27] Ballen KK. New trends in umbilical cord blood transplantation. *Blood*. 2005; 105(10):3786-92.
- [28] Ferry C, Socié G. Busulfan-cyclophosphamide versus total body irradiation-cyclophosphamide as preparative regimen before allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia: what have we learned? *Exp Hematol*. 2003; 31(12):1182-6.
- [29] Tutschka PJ, Copelan EA, Klein JP. Bone marrow transplantation for leukemia following a new busulfan and cyclophosphamide regimen. *Blood*. 1987; 70(5):1382-8.
- [30] Kashyap A, Wingard J, Cagnoni P, Roy J, Tarantolo S, Hu W, Blume K, Niland J, Palmer JM, Vaughan W, Fernandez H, Champlin R, Forman S, Andersson BS. Intravenous versus oral busulfan as part of a busulfan/cyclophosphamide preparative regimen for allogeneic hematopoietic stem cell transplantation: decreased incidence of hepatic venoocclusive disease (HVD), HVD-related mortality, and overall 100-day mortality. *Biol Blood Marrow Transplant*. 2002; 8(9):493-500.
- [31] Clift RA, Buckner CD, Appelbaum FR, Bearman SI, Petersen FB, Fisher LD, Anasetti C, Beatty P, Bensinger WI, Doney K, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. *Blood*. 1990; 76(9):1867-71.
- [32] Kolb HJ, Mittermüller J, Clemm C, Holler E, Ledderose G, Brehm G, Heim M, Wilmanns W. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. *Blood*. 1990; 76(12):2462-5.
- [33] McSweeney PA, Niederwieser D, Shizuru JA, Sandmaier BM, Molina AJ, Maloney DG, Chauncey TR, Gooley TA, Hegenbart U, Nash RA, Radich J, Wagner JL, Minor S, Appelbaum FR, Bensinger WI, Bryant E, Flowers ME, Georges GE, Grumet FC, Kiem HP, Torok-Storb B, Yu C, Blume KG, Storb RF. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood*. 2001; 97(11):3390-400.
- [34] Markiewicz M, Siekiera U, Dzierzak-Mietla M, Zielinska P, Kyrz-Krzemien S. The impact of H-Y mismatches on results of HLA-matched unrelated allogeneic hematopoietic stem cell transplantation. *Transplant Proc* 2010; 42(8):3297-300.

- [35] Remberger M, Storer B, Ringdén O, Anasetti C. Association between pretransplant Thymoglobulin and reduced non-relapse mortality rate after marrow transplantation from unrelated donors. *Bone Marrow Transplant.* 2002; 29(5):391-7.
- [36] Savani BN, Griffith ML, Jagasia S, Lee SJ. How I treat late effects in adults after allogeneic stem cell transplantation. *Blood.* 2011; 117(11):3002-9.
- [37] Mattsson J, Uzunel M, Tammik L, Aschan J, Ringdén O. Leukemia lineage-specific chimerism analysis is a sensitive predictor of relapse in patients with acute myeloid leukemia and myelodysplastic syndrome after allogeneic stem cell transplantation. *Leukemia.* 2001; 15(12):1976-85.
- [38] Dazzi F, Szydlo RM, Craddock C, Cross NC, Kaeda J, Chase A, Olavarria E, van Rhee F, Kanfer E, Apperley JF, Goldman JM. Comparison of single-dose and escalating-dose regimens of donor lymphocyte infusion for relapse after allografting for chronic myeloid leukemia. *Blood.* 2000; 95(1):67-71.
- [39] Childs R, Chernoff A, Contentin N, Bahceci E, Schrupp D, Leitman S, Read EJ, Tisdale J, Dunbar C, Linehan WM, Young NS, Barrett AJ. Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. *N Engl J Med.* 2000; 343(11):750-8.
- [40] Barkholt L, Bregni M, Remberger M, Blaise D, Peccatori J, Massenkeil G, Pedrazzoli P, Zambelli A, Bay JO, Francois S, Martino R, Bengala C, Brune M, Lenhoff S, Porcellini A, Falda M, Siena S, Demirer T, Niederwieser D, Ringdén O; French ITAC group and the EBMT Solid Tumour Working Party. Allogeneic haematopoietic stem cell transplantation for metastatic renal carcinoma in Europe. *Ann Oncol.*; 17(7):1134-40.
- [41] Li ZH, Liao W, Cui XL, Zhao Q, Liu M, Chen YH, Liu TS, Liu NL, Wang F, Yi Y, Shao NS. Intravenous transplantation of allogeneic bone marrow mesenchymal stem cells and its directional migration to the necrotic femoral head. *Int J Med Sci.* 2011; 8(1): 74-83.