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Stem cell transplantation – an overview of clinic-based data and practice in the era of new drugs

Transplantacija matičnih ćelija – pregled podataka iz kliničke prakse u eri novih lekova

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Abstract

Hematopoietic stem cell transplantation (HSCT) has been the therapy of choice for treating some hematologic malignancies and selected non-malignant disorders for decades. With the introduction of novel immunotherapeutic and cell-mediated approaches, the role of autologous HSCT (auto-HSCT) and allogeneic HSCT (allo-HSCT) should be redefined. Auto-HSCT remains the standard of treatment for multiple myeloma, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. The use of novel agents, including proteasome inhibitors, immunomodulatory drugs, monoclonal and bispecific antibodies, enhances the intensity and efficacy of the therapeutic response and opens debate on an optimized timing for HSCT. Allo-HSCT represents the most effective type of adoptive immunotherapy, ensuring complete and long-term hematopoietic reconstitution, often accompanied by the graft-versus-leukemia effect. It remains the main curative treatment for acute leukemias, high-risk myelodysplastic and myeloproliferative syndromes, and severe aplastic anemia. Improvements in stem cell (SC) donor selection, *ex vivo* manipulations of harvested cells, and graft engineering with superior immune monitoring have broadened and expanded their applicability, while improving safety and clinical outcome. Despite rapid progress in cellular and other immunotherapies, HSCT continues to play an essential role in the treatment of numerous hematologic disorders. A combination of HSCT with novel drugs and other immunotherapies offers the potential for personalized and safer treatment with long-term positive clinical outcomes, ensuring that HSCT remains a highly relevant method in modern medicine. The aim of this review was to summarize current biological concepts of SCs, as well as important advances in the rapidly developing fields of SC research, and to determine the place and efficacy of HSCT nowadays, in the era of new therapeutic approaches and agents.

Keywords:
allografts; cryopreservation; hematologic diseases; immunotherapy; multiple myeloma; stem cells; transplantation, autologous.

Apstrakt

Transplantacija hematopoetskih matičnih ćelija (*hematopoietic stem cell transplantion* – HSCT) već decenijama predstavlja terapiju izbora u lečenju pojedinih hematoloških maligniteta i nekih nemalignih poremećaja. Uvođenjem novih imunoterapijskih i ćelijama-posredovanih pristupa trebalo bi da bude redefinisana uloga autologne HSCT (auto-HSCT) i alogene HSCT (alo-HSCT). Auto-HSCT i dalje ostaje standard u lečenju multiplog mijeloma, Hočkinovog limfoma i ne-Hočkinovog limfoma. Primena novih medikamenata, uključujući inhibitore proteazoma, imunomodulacijske lekove, monoklonska i bispecifična antitela, povećava intenzitet i efikasnost terapijskog odgovora na HSCT i otvara raspravu o optimalnom vremenu za primenu HSCT. Alo-HSCT predstavlja

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najefikasniji oblik adoptivne imunoterapije, obezbeđujući kompletnu i dugotrajnu hematopoetsku rekonstituciju, neretko praćenu efektom "kalem protiv leukemije" (*graft-versus-leukemia*). Ona ostaje primarni kurativni vid lečenja akutnih leukemija, visoko-rizičnih mijelodisplastičnih i mijeloproliferativnih sindroma, kao i teške aplastične anemije. Poboljšanja u izboru donora matičnih ćelija (*stem cell* – SC), *ex vivo* manipulaciji prikupljenih ćelija, kao i inženjering grafta uz napredni imunski monitoring, proširila su i unapredila primenljivost ove terapije uz istovremeno povećanje bezbednosti i poboljšanje kliničkog ishoda. Uprkos brzom napretku u oblasti ćelijama posredovane i drugim agensima posredovane imunoterapije, HSCT i dalje ima ključnu ulogu u lečenju pojedinih hematoloških poremećaja. Kombinacija HSCT sa novim lekovima i drugim vidovima imunoterapije pruža mogućnost personalizovanog i bezbednijeg lečenja sa dugotrajnim povoljnim kliničkim ishodima, i obezbeđuje da HSCT ostane visoko relevantan metod u savremenoj medicini. Cilj ovog rada bio je da se sumiraju trenutni biološki koncepti SC, kao i bitna dostignuća na istraživačkim poljima u oblasti SC koja se brzo razvijaju, i da se odredi mesto i efikasnost HSCT danas, u eri novih terapijskih pristupa i agenasa.

Ključne reči:
alograft; kriokonzervacija; hematološke bolesti; imunoterapija; multipli mijelom; ćelije, matične; transplantacija, autologna.

Introduction

Stem cells (SCs) are defined as cells with a unique ability for self-renewal, high proliferative capacity, and the potential to differentiate into mature blood or somatic cells, such as osteocytes, chondrocytes, hepatocytes, myocytes, cardiomyocytes, and even endothelial cells. The increasing clinical use of various cell-mediated therapeutic methods over the past decades has resulted in a growing demand for both hematopoietic SCs (HSCs) and the need to adapt and improve operating procedures to minimize cellular injury during collection, purification, and cryopreservation. A critical aspect of cell harvesting is obtaining improved SC yield, purity, and viability. The objective of fundamental and clinical cryoinvestigations is to decrease cellular damage during freeze/thaw procedures (cryoinjury). Although SC clinical use has become routine, a large number of questions related to optimal cell harvesting protocols, *ex vivo* processing, and cryopreservation remain unresolved [1–3].

Since the initial treatments with HSC transplants (HSCT), considerable changes and improvements have been made in the kind of medications used for peritransplant treatment of patients. In addition, new approaches and agents/drugs have recently been introduced for the therapy of various hematological diseases and disorders. For instance, the use of autologous HSCT (auto-HSCT) has long been a standard method for transplant-eligible patients. However, its status in treatment should be redefined due to the introduction of agents such as proteasome inhibitors, immunomodulatory drugs, monoclonal or bispecific antibodies (Abs), and chimeric antigen receptor T (CAR-T) cellular therapies [2–6].

The purpose of this paper is to recapitulate data in the field of conceptual aspects of SCs harvesting and extracorporeal "graft-engineering" systems adapted to specific cell categories. Moreover, some practical aspects of the place and justification of HSCTs in the era of new drugs and other biologically active agents will be briefly reviewed.

Stem cells – biology and *ex vivo* manipulations

The biology of various divisions of SCs is a fascinating and constantly expanding field of biomedicine that examines and describes both the fundamental properties of these cells, as well as the possibility and effectiveness of their therapeutic use in cell transplant and regenerative medicine [1–5]. There are different types and sources of SCs: embryonic SCs (ESCs – concerning their therapeutic use, ongoing regulations/directions are required), adult SCs (ASCs) or tissue-specific SCs (e.g., HSCs, and mesenchymal SCs – MSCs, etc.), as well as induced pluripotent SCs (iPSCs) – produced through "HSCs reprogramming" of somatic cells back into a pluri(multi)potent stage/phase. MSCs are important due to immunomodulation competence and the ability to differentiate into numerous cell types of mesodermal origin (tissue repair) [2, 6–14].

Cytopoiesis is a continuous biological process of producing a large number of "daughter cells" from the compartment of a single or solitary "parent" SC. The original explanation and description of SCs – that they are exclusive, high-class cells at an early developing stage, characterized by an almost limitless self-renewal ability (long-term possibility to create identical copies of themselves), high proliferative capacity, and extensive potential for differentiation into specialized and ever more mature cells of different lineages in the body – remains unsurpassed [2–10].

Thus, SCs are the "key" cells in the body functioning as special "antecedent" cells or precursors that precede (hemo)biological events or cellular evolution, producing a large quantity (proliferation) of mature (differentiation) cells within tissues, while simultaneously retaining the ability to reproduce themselves (self-renewal). This event is precisely regulated by intrinsic genetic/molecular pathways, which can be influenced by external signals from the extracellular matrix (ECM), as well as by the microenvironment provided by stromal cells [6–14].

Owing to the phenomenon of self-renewal, SCs maintain the constancy of their own population under steady-state conditions, but also in conditions when that physiological balance is disturbed – up to a certain limit. Through differentiation, primitive SCs create a "wide-ranging" series of less primitive cells: firstly, different pluri(multi)potent SCs with a somewhat decreased self-renewal ability, and then cells determined for more or just one cell lineage, which have a very moderate or no potential for self-renewal. To further clarify SCs, an "up-to-date" characteristic has been added–cell plas-

ticity (more precisely, intersystemic plasticity)–which is particularly important for their clinical application in regenerative medicine [2, 7–16].

Concisely, the most primitive SCs give rise to repopulation of the recipient's bone marrow (BM)–engraftment with the following complete and long-term reconstitution of hematopoiesis. They are also capable of "colonizing" targeted/damaged tissues ("homing")–by following "transdifferentiation" into the cell lineages of host organ, including collateral vessel formation ("neovascularization") [2, 17–22].

The use of HSCT is a highly specialized and often life-saving curative procedure in which a patient receives auto-HSCs or allogeneic HSCs (allo-HSCs) following high-dose chemotherapy (HDCT), and less frequently chemoradiotherapy, in order to replace damaged BM with healthy cells. In an autologous setting (auto-HSCT), a patient receives their own HSCs following HDCT. Allo-HSCT is a therapeutic method of replacing the patient's hematopoietic tissue with donor "blood-forming" cells/tissue, i.e., HSCs. It represents the concept of applying chemotherapy/radiotherapy with immunosuppressive treatment, after which donor HSCs are applied to the patient with high-risk hemato-malignancies [2–6].

In practice, HSCT represents a curative method of treating malignant disorders, such as Hodgkin's lymphoma (HL) and non-HL (NHL), multiple myeloma (MM), acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), myelodysplastic syndrome, and myeloproliferative neoplasms (MPN) [6, 23–34]. Transplants are also indicated for the treatment of some non-malignant diseases and immune-mediated disorders, such as severe aplastic anemia and multiple sclerosis (MS) [2, 35–41].

Stem cell collection

In practice, SCs can be collected by multiple aspirations from BM, by harvesting mononuclear cells (MNCs) from peripheral blood (PB) after a mobilizing regimen, or by isolation from umbilical cord blood. Typically, the use of BM- or PB-derived grafts is a standard method in adult patients, whereas umbilical cord blood transplants have shown promising results, particularly in the pediatric setting [41–45].

Historically, BM was the primary source of SCs for transplantation in both experimental and clinical settings, obtained through multiple aspirations from the posterior and anterior iliac crests and, rarely, from the sternum. Nowadays, SCs are predominantly harvested from PB, accounting for ≥ 80% of HSCTs, after a mobilization regimen, using chemotherapy and/or granulocyte colony-stimulating factor (G-CSF), seldom in combination with plerixafor (mozobil) [2, 6, 24, 26, 42]. The use of G-CSF plus plerixafor increases the ratio of patients who respond to the cell mobilization ("good-mobilizers" – approximately 95% of cell harvestings) and enables the collection of enough cells for auto-HSCT (including patients with "mobilization-failure" or "poor-responders") [24].

Determining the best possible time for SC-harvesting from PB is the most critical event. For allogeneic donors, the first apheresis is regularly on the fifth day of G-CSF application. However, deciding on the optimal timing for autologous collection from patients who are primed by chemotherapy plus G-CSF is more complex and challenging. The circulating $CD34^+$ cells count evidently correlates with optimized harvesting time and SC quantity [target $CD34^+$ yield ≥ 2–5×10^6 cells/kg of patient's body mass (bm) in the harvest]. Nowadays, it is accepted that optimal timing to begin cell collection is when the number of $CD34^+$ cells is ≥ 20–40/μL of the patient's PB [3–6, 24, 41].

Our results confirmed the high-level efficacy of the large volume leukapheresis (LVL). For the approximately 90% of patients using one LVL, the mean $CD34^+$ yield was 8.4×10^6 cells/kg bm (allo-HSCT) and 5.5×10^6 cells/kg bm (auto-HSCT), respectively [2–4, 44]. Finally, in the group of patients requiring plerixafor, the use of the G-CSF plus plerixafor protocol reduced the rate of "poor-responders" and provided an adequate cell dose (mean $CD34^+$ cell yield was 7.6×10^6 cells/kg bm – to be able to perform a tandem auto-HSCT as well) with a superior therapeutic potential and safety profile of treatment [24].

Stem cell cryopreservation

The saving/banking of living cells, such as SCs, in a frozen state (cryopreservation) is required when cells appear to be biologically, chemically, or thermally unstable after liquid-state storage. Its key aim is to obtain better-quality cell count and viability recovery after thawing. Although SC-cryopreservation is nowadays a standard technique, recent cryoinvestigations recommend that freezing strategies be revised to minimize cryoinjuries and maximize cell recovery. Cryoinjuries result from the extensive cellular dehydration or "solution effect" and/or massive intracellular ice crystallization or "mechanical damage" [2, 4, 46–50].

The use of programmed or controlled-rate freezing, which ensures a precisely defined cooling rate, is a time-consuming process that requires high-level technical knowledge. The choice of an optimal freezing rate – specific for each cell type and cryobiosystem – should be determined. In practice, the cooling rate should be sufficiently rapid to prevent "solution effect", yet slow enough to allow possible water efflux from the cells and following "mechanical damage" [2, 6, 50]. Uncontrolled-rate technique ("dump-freezing") is less costly because it does not require a complex programmed freezing device. However, it has been confirmed that controlled-rate freezing systems are superior, as they provide better quantitative, morphological, ultrastructural, and functional cell recovery during cryopreservation and following thawing [45–50]. In addition, satisfactory numerical and functional recovery of cryopreserved SCs is achieved only when an appropriate cryoprotectant – most commonly dimethyl sulfoxide (DMSO) for SC cryopreservation—is added to the cryobiosystem at an optimal final concentration. Cryoprotectants express protective effects and consequences by decreasing cellular thermal damage, i.e., by reducing cell dehydration and intracellular ice crystallization [2, 50].

As previously demonstrated in our cryoinvestigations using a controlled-rate freezing system, the recovery of

committed hematopoietic progenitors – colony-forming unit (CFU)–spleen (CFU-Sd12) and CFU – granulocyte-macrophage (CFU-GM) – was improved in the presence of 5% DMSO [46]. On the other hand, we confirmed that the recovery of very primitive pluripotent SCs with marrow repopulating ability was better when 10% DMSO was used. Thus, our cryoinvestigation suggested various cryobiological characteristics and requirements of marrow repopulating ability cells compared with committed progenitors [46]. Finally, our early clinical studies showed that therapeutic use of controlled-rate cryopreserved SCs (10% DMSO) in the therapy of hemato-oncological patients resulted in high cell recovery and rapid post-transplant hematopoietic reconstitution, with neutrophil recovery occurring on average by day 11 and platelet recovery by day 13 [2, 24, 44].

The most frequent indications for auto-HSCT in hematology

As previously pointed out, auto-HSCT is a common procedure in hematology, primarily used to treat certain blood cancers. The main purpose of auto-HSCT is to "rescue" the patient's BM after damage caused by HDCT. Although HDCT is highly effective in eradicating malignant cells, it also destroys the healthy, "blood-forming" SCs, i.e., HSCs, in the BM [2–6].

In hematology, the most common indications for auto-HSCT are MM, HL, and NHL. In the treatment of patients with MM, auto-HSCT is often a standard part of the initial treatment for eligible patients, aiming to consolidate the initial therapeutic response. Conditioning regimen with standard high-dose melphalan (HD-Mel) is used to achieve a deep and long-lasting remission [51]. Based on the most recent data from the European Society for Blood and Marrow Transplantation (EBMT), MM is the most frequent indication for auto-HSCT. According to the 2023 EBMT report on HSCT and cellular therapies, plasma cell disorders, which primarily consist of MM, accounted for 58.2% of all auto-HSCT performed in Europe in 2023. The other main indications for autologous transplants in 2023 were lymphomas (32.2%) and solid tumors (6.6%). Among lymphomas are HL and NHL [52]. Additionally, auto-HSCc is a standard treatment for HL patients who have relapsed or whose disease is refractory to initial chemotherapy (relapsed/refractory – r/r HL), which accounts for approximately 40% of initial patients with this diagnosis [53]. Finally, auto-HSCT is frequently used as salvage therapy for patients with r/r NHL, or can also be used as consolidative treatment for high-risk patients, such as those with mantle cell lymphoma (MCL) or anaplastic large cell (ALC) lymphoma [54].

The role of auto-HSCT in MM, HL, and NHL in the era of new drugs and cellular therapies

Multiple myeloma

The field of MM treatment is constantly evolving, with the introduction of new drugs significantly impacting the role of auto-HSCT. While auto-HSCT has long been a standard of care for transplant-eligible patients (up to 65–70 years), its place in the treatment paradigm is being redefined by novel agents such as proteasome inhibitors, immunomodulatory drugs, monoclonal Abs, bispecific Abs, and CAR-T cellular therapies [55].

Despite all novel approaches in MM, an auto-HSCT remains a standard of care for many patients, since it is highly effective, particularly for younger and fit patients with newly diagnosed MM [56]. It is well known that it can provide deep and durable responses, which translate to longer progression-free survival. Some studies have even shown an overall survival (OS) benefit [57].

In the course of first-line treatment, auto-HSCT is often performed after a period of induction therapy. Initial treatment, which includes triple or, in high-risk patients, quadruplet combinations of new drugs, optimizes initial therapeutic response before the transplant procedure and changes the paradigm "when" and "how" to perform an auto-HSCT in MM patients.

There are a few pillars in the patient journey from diagnosis to possible optimal treatment response, and they are described in the passages that follow.

Improved induction with novel agents in combined regimens, including proteasome inhibitors (e.g., bortezomib, carfilzomib), immunomodulatory drugs (e.g., lenalidomide – LEN), and monoclonal Ab (e.g., daratumumab), is used before auto-HSCT. These drugs achieve a deeper initial response before the transplant.

The role of HD-Mel (200 mg/m^2) with possible addition of a new drug in the conditioning regimen before application of autologous HSCs in a single or tandem setting in high-risk patient [58].

New drugs are also used after auto-HSCT for maintenance therapy to prolong remission. This includes drugs like the immunomodulatory drug LEN, and ongoing research is exploring other options to maintain the depth of the post-transplant response [59].

The debate on upfront vs. delayed auto-HSCT: the excellent results achieved with novel drug combinations have led to a discussion regarding whether auto-HSCT should be performed right after induction therapy (upfront) or delayed until disease relapse. While some trials have shown a benefit to upfront auto-HSCT in terms of progression-free survival, the OS benefit is not always clear. This makes the decision highly personalized as part of an evidence-based approach in the patient's specific case [60].

The use of new immunotherapies like CAR-T-cell therapy and bispecific Abs is emerging as a highly effective option, particularly for patients with r/r MM [61]. These therapies are currently being explored for earlier use in the treatment pathway and may further impact the role of auto-HSCT in the future [62].

Hodgkin's lymphoma

In the r/r HL, new drugs such as brentuximab vedotin (BV) and checkpoint inhibitors play a great role as novel

treatment options [63]. Auto-HSCT exerts its principal benefit as consolidation therapy, particularly in achieving a second remission in chemosensitive r/r HL patients. The main purpose of auto-HSCT in these cases is to allow the administration of HDCT. The consolidation with BV after auto-HSCT in HL patients with high risk of relapse is the main achievement of this combined approach [64]. After treatment failure with BV, other options in r/r HL are different checkpoint inhibitors like nivolumab, pembrolizumab, and ipilimumab [65]. After relapse with all previously explained approaches in r/r HL, allo-HSCT could be the only reasonable treatment option. This type of transplant provides the additional benefit of creating a "new" immune system that may be able to recognize and fight any remaining lymphoma cells. However, it also carries a higher risk of complications, such as graft-versus-host disease (GvHD). The decision to use a different type of HSCT depends on various factors, including remission status, comorbidities, and the patient's preferences. While newer therapies are emerging, SC transplantation continues to play a vital role in the management of r/r HL.

Non-Hodgkin's lymphoma

Auto-HSCT plays a crucial role in the treatment of many subtypes of NHL, but its use and effectiveness vary substantially depending on the specific type of lymphoma. The biological nature of NHL is extremely heterogeneous and includes numerous pathohistological entities, 85% of which are of B-cell origin. Unlike in HL, where the treatment is more standardized, the diverse nature of NHL requires a tailored approach.

The main purpose of auto-HSCT in NHL is to enable the use of HDCT [54]. The most common representatives of aggressive B-cell lymphomas, which are candidates for auto-HSCT, are diffuse large B-cell lymphoma (DLBCL), MCL, indolent follicular lymphoma (FL), and, concerning T-cell types, peripheral T-cell lymphoma. Here is a summary of the role of auto-HSCT in these NHL subtypes.

Diffuse large B-cell lymphoma

First-line treatment: for most patients, DLBCL is successfully treated with standard immunochemotherapy (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone – R-CHOP), achieving remission rates of approximately 60–70%. Auto-HSCT is not standard of care as consolidation therapy in first remission [66].

r/r DLBCL is a platform where auto-HSCT is considered a standard and potentially curative treatment option. However, before undergoing auto-HSCT, the disease status of r/r DLBCL must be chemosensitive after receiving salvage therapy. In chemotherapy-refractory patients, some other treatment options, such as monoclonal Abs-drug conjugates (e.g., polatuzumab vedotin), bispecific Abs (e.g., glofitamab), or CAR-T cells, provide an adequate therapeutic response [67].

Mantle cell lymphoma

Since MCL is a highly aggressive disease, consolidation of first remission with auto-HSCT has represented the standard of care for almost two decades [68]. The goal is to extend the duration of the first remission and improve long-term survival. This approach is a standard of care and an important part of treatment for many younger patients with MCL [69]. In chemo-refractory patients, the Bruton tyrosine kinase inhibitor ibrutinib or the immunomodulatory drug LEN can be treatment options, sometimes as a "bridge" to allo-HSCT. For patients with r/r MCL, allo-HSCT may also be considered. This approach is more intense and bears a higher risk, but it can be effective due to the graft-versus-lymphoma effect, where the donor's immune cells attack the remaining tumor cells.

Follicular lymphoma

Auto-HSCT is not typically part of the initial treatment for FL, which is often managed with less intensive therapies. For patients with r/r FL who no longer respond to other treatments, auto-HSCT can be used to achieve a long-lasting remission. Allo-HSCT may also be an option for a small, selected group of patients, particularly those with a high-risk FL or those who have failed auto-HSCT [70].

Key factors that historically predicted a good outcome with auto-HSCT in r/r FL include chemosensitivity to salvage therapy. Namely, patients who achieve a complete or partial response after a salvage chemotherapy regimen before transplant generally have better outcomes [71]. Patients who relapse more than 2 years after their initial therapy tend to have better outcomes with auto-HSCT compared to those with early relapse (within 24 months, also known as progression of disease within 24 months – POD24). However, some studies have shown that auto-HSCT can still be a valuable option even for patients with POD24, leading to improved survival [72]. Studies have found that patients who were sensitive to rituximab-based immune-chemotherapy prior to auto-HSCT had significantly better outcomes. The introduction of new drugs and cellular therapies has dramatically altered the treatment landscape for r/r FL. These new options have provided effective alternatives to intensive chemotherapy and auto-HSCT, particularly for patients who are not suitable candidates for a transplant or those who have failed prior therapies or were completely refractory. The use of targeted therapies, such as Bruton tyrosine kinase inhibitors, phosphoinositide 3-kinase inhibitors, and enhancer of zeste homolog 2 inhibitors, has become a cornerstone of treatment for r/r FL. These agents offer durable responses with a more favorable toxicity profile compared to traditional chemotherapy. The novel cellular approach, like CAR-T-cell therapy, has emerged as a powerful option for patients with multiply relapsed FL. It has shown impressive response rates, even in patients who have failed multiple prior lines of therapy, including rituximab and other targeted drugs. Additionally, a new class of immunotherapy called bispecific Abs is also

showing promise in r/r FL, offering another alternative to traditional treatments [73].

Peripheral T-cell lymphomas

Peripheral T-cell lymphomas are generally more aggressive and have a poorer prognosis than B-cell lymphomas. In many cases, auto-HSCT may be used as consolidation of first remission to prevent relapse. For patients with relapsed peripheral T-cell lymphoma, an allo-HSCT is often considered due to the role of donor T cells for the potential curative graft-versus-lymphoma effect [74].

The most frequent indications for allo-HSCT in hematology

Allo-HSCT works by replacing a patient's unhealthy or damaged BM with healthy donor HSCs, which then produce a new, well-functioning immune system. This new immune system can recognize and destroy remaining cancer cells, a process known as the graft-versus-tumor or graft-versus-leukemia (GvL) effect. The most frequent indications for allo-HSCT among hematologic disorders are malignant disorders, such as leukemias, followed by other hematologic malignancies and non-malignant disorders like BM failure syndromes. As *per* EBMT's last activity survey, AML is the most common indication for allo-HSCT and accounts for more than one-third of allo-HSCT [75].

Malignant disorders as indications for allo-HSCT

As mentioned, common indications for clinical application of allo-HSCT among hematological disorders include various malignant diseases, as presented below: in patients with AML who have intermediate- or high-risk disease in their first remission, or in those with relapsed disease in second or subsequent complete remission, allo-HSCT is considered the only curative option [76].

ALL with high-risk characteristics defined by well-established criteria is an indication for allo-HSCT, both in children and adults. For patients with relapsed disease in second or subsequent complete remission, allo-HSCT is also a reasonable treatment option [77]. In patients with *BCR-ABL+* ALL, treatment with second- or third-generation tyrosine kinase inhibitors may be preferred in certain circumstances.

Myelodysplastic syndrome with intermediate-2 to high-risk characteristics has a significant chance of transforming into AML and is a typical indication for allo-HSCT as a primary treatment option [78].

Myelofibrosis and other Philadelphia-negative MPN with high-risk scores and a high risk of disease progression are also standard indications for allo-HSCT as the only potentially curative treatment [79].

Chronic myeloid leukemia became potentially curable in the era of tyrosine kinase inhibitors, first to third generation. These drugs have largely replaced allo-HSCT for chronic myeloid leukemia, but when patients are intolerant or resistant to these drugs, it is still a reasonable treatment option [80].

The r/r lymphomas, especially when a prior auto-HSCT has failed, can be reasonable candidates for allo-HSCT, taking into consideration all risk factors connected to patients and disease status [81].

Non-malignant disorders as indications for allo-HSCT

Severe aplastic anemia as a BM failure syndrome is a significant indication for allo-HSCT, particularly for younger patients with a fully matched sibling donor. Congenital BM failure syndromes like Fanconi anemia and severe congenital neutropenia are also treated with allo-HSCT. Primary immunodeficiency syndromes, as severe inherited immune system disorders, can also be cured with allo-HSCT [82].

Congenital anemias like thalassemia major and sickle cell anemia can be treated with allo-HSCT as a curative treatment, especially in countries where these diseases are common genetic disorders [82].

Taking into account all the above, we must point out that allo-HSCT represents the most powerful form of adoptive immunotherapy for cancer, particularly for hematologic malignancies. Its curative potential is not solely linked to the HDCT +/- radiotherapy as part of the conditioning regimen, which is used to eliminate malignant cells, but is also present due to the GvL effect. Namely, allo-HSCT functions as an adoptive immunotherapy, and its mechanisms are based on the mentioned GvL effect.

The settings and application of adoptive immunotherapy

Adoptive immunotherapy is a form of treatment that uses the cells of our immune system (collected by apheresis, *ex vivo* modified, and then reinfused) to eliminate some tumor/cancer cells. In a broader sense, the term adoptive immunotherapy also includes the application of donor immunocompetent cells in order to achieve an anti-tumor effect (e.g., GvL effect).

The main aspects of adoptive immunotherapy

Adoptive immunotherapy is a form of treatment that uses donor immune cells, such as T cells, to fight against the patient's malignant cells [83]. In allo-HSCT, the "graft" of donor SCs is not just a source of new blood cells; it is a source of an entirely new immune system for the patient. This new immune system, derived from the donor, has a potent anti-tumor effect. The main principle is that the donor's immune cells recognize the patient's malignant cells as "foreign". This occurs because malignant cells, although originating from the patient, may express unique antigens or exhibit altered patterns of antigen presentation. Donor T cells and other immune cells, such as natural killer (NK) cells, can mount an immune response against the patient's malignant cells, leading to their destruction.

A few crucial points of the model of adoptive immunotherapy

The transfer of immunocompetent cells since the donor graft contains T cells, NK cells, and other immune cells that are already "programmed" to fight infections and recognize foreign threats, presents the mainstay of adoptive immunotherapy. These immune cells, infused into the patient, are able to attack the malignant clone directly [84].

The creation of a new, healthy immune system, as donor HSCs engraft in the patient's BM niche and begin to produce all types of blood cells, including a new, healthy population of cells and other immune cells, is the goal of adoptive immunotherapy. This new immune system can provide long-term surveillance against the disease relapse. Reconstitution of some donor immune cells is crucial for protecting a patient from disease relapse [85].

Controlling alloreactivity is crucial after allo-HSCT with strong monitoring and management of immunosuppressive therapy. Despite auto-HSCT, which provides autologous support with HSCs after a high-dose conditioning regimen, allo-HSC can produce a graft-versus-tumor effect. This effect represents the immune response of the donor's cells against the patient's allo-antigens, which can be a double-edged sword, leading to both a beneficial GvL effect and a dangerous side effect known as GvHD. Therefore, the GvL effect is the primary mechanism by which allo-HSCT provides its long-term curative benefit [86]. In the context of alloreactivity, GvHD is also one of the earliest and most powerful effects that can be present in a mild-to-moderate form that protects patients from leukemia relapse. Unfortunately, severe GvHD is a life-threatening complication that targets the patient's skin, lung, liver, upper and lower gastrointestinal tract, and all other healthy tissues [86].

In the setting of early leukemia relapse after allo-HSCT or a decrease in full donor chimerism, the additional application of donor lymphocytes, so-called donor lymphocyte infusion, can provide additional GvL effect. Namely, the infusion of more donor lymphocytes can induce a remission, even without additional chemotherapy. This shows that the donor immune cells, not just the conditioning regimen, are capable of eradicating the leukemia [87]. In order to deplete alpha-beta T-cell receptor (TCR) T lymphocytes while preserving gamma-delta TCR T lymphocytes, *ex vivo* graft manipulation or T-cell depletion has shown that removal of T cells from the donor graft before transplantation decreases the incidence of GvHD. However, this also leads to a significant increase in the risk of leukemia relapse, further proving that the donor T cells are crucial for the GvL effect [87–89].

Moreover, the type of conditioning regimen can either potentiate myeloablation in the myeloablative setting, so-called myeloablative conditioning, or enhance immunogenicity in a reduced-intensity setting [reduced-intensity conditioning (RIC) regimens]. The development of RIC regimens – also known as "mini-transplants" – provides a powerful GvL effect. These regimens use lower doses of chemotherapy that are sufficient to allow donor cell engraftment, but not to fully eradicate the malignant cells. The primary anti-tumor effect is then left to the donor's immune cells. This approach has made allo-HSCT an option for older and less fit patients [78].

As previously mentioned, the GvL effect can be potentiated by cellular mediators such as T cells (cytotoxic T-lymphocytes), NK cells, which can kill leukemia cells without prior sensitization, and are particularly important in haploidentical transplants, and by B cells, dendritic cells, and other immune cells that also contribute to the GvL effect by supporting and modulating the T-cell response [86, 87].

Our data also show that immune reconstitution after allo-HSCT is pivotal in achieving favorable long-term outcomes by influencing the rates of infection, GvHD, and relapse. Namely, we evaluated the clinical impact of immune reconstitution on NK cells on day +90 after allo-HSCT, as well as $CD4^+$ T cells, $CD8^+$ T cells, B cells, and NKT cells by performing a landmark analysis in event-free patients. Our results showed that high NK cell counts on day +90 (>178 cells/μL) were associated with improved OS ($p = 0.039$) and lower rates of non-relapse mortality [1-year cumulative incidence of 5.7% vs. 31.4%, hazard ratio 0.16, 95% confidence interval: 0.04–0.69, $p = 0.014$] after T-cell-depleted allo-HSCT [85].

Conclusion

Auto-HSCT continues to be a standard treatment to consolidate first-line response for many patients with MM. However, its role is increasingly being integrated with and influenced by a growing number of novel drugs. These new agents are not only making auto-HSCT more effective but are also providing additional treatment options, leading to more personalized and long-lasting outcomes for multiple myeloma patients. Like in Hodgkin's lymphoma, the role of auto-HSCT in non-Hodgkin's lymphoma is being influenced by the emergence of new, highly effective therapies. Targeted drugs, CAR T-cell therapy, and bispecific antibodies are changing the treatment sequence and raising questions about whether transplantation can be delayed or even avoided for some patients. Auto-HSCT is generally reserved for lymphoma patients with relapsed or refractory disease who are chemosensitive following salvage therapy, and for consolidation of first remission in high-risk patients to improve the chances of long-term survival.

Allo-HSCT is a highly effective form of adoptive immunotherapy because it provides a new, healthy immune system capable of recognizing and destroying a patient's malignant cells. The most frequent indications among malignant disorders are acute leukemias, and in non-malignant settings, severe aplastic anemia and severe immunodeficiency. The transfer of immunocompetent cells from the donor graft presents the backbone of adoptive immunotherapy. A strong graft-versus-leukemia effect, mediated by donor immune cells, is a fundamental mechanism of this curative treatment, demonstrating the power of the immune system to combat aggressive hematologic malignant disorders.

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