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Review

Role of Autologous Haemopoietic Transplantation in Leukemias, When to Consider It, 2026

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Abstract

This review aims to provide comprehensive and practical information on the once-nearly-forgotten but now resurgent roles and trends of autologous transplantation in leukemias. We seek to categorize when it is necessary as a first-line treatment (plasma cell leukemia) and to identify well-defined patient subgroups (such as certain types with intermediate prognosis in AML, APL second remission, etc.) in which autologous transplantation might be comparably or even slightly more effective than allogeneic transplantation, not only in frail patients. In some leukemias, such as CLL, autologous transplantation still does not play a role. Attempts to achieve anti-leukaemic effects in autologous settings have proven largely ineffective, but new approaches might be promising. Newer cell therapies (such as CAR-T) are significantly more effective, and the same applies to in vitro graft purging. However, this area has been investigated relatively recently in an innovative manner, using specific graft pretreatments that may also stimulate anti-leukemic immune responses in autologous cases.

Keywords: autologous transplantation; acute myeloid leukemia; plasma cell leukemia; innovative approaches to improve results in autologous settings

Introduction

History

Decades ago, mainly due to Gorin's, Burnett's and Stuart's [1,2] excellent approaches and efforts, autologous stem cell transplantation was considered a powerful alternative to allogeneic transplantation modalities in AML (sometimes instead of post-induction (cytosine arabinoside type therapies). This concept was supported primarily because of the limited availability of compatible donors at the time, also due to the higher early transplant-related mortality associated with allogeneic procedures during that period, and the costs of post-induction therapies for acute leukemias [3].

There were special early recommendations regarding AML autologous transplantation, including conditioning (firstly TBI-cyclophosphamide, later Flu-Mel, and, later, Bu-Mel, etc.) and the timing of the autologous transplant, not too early (later, this concept changed a lot) after post-induction treatment [1,2,4]. Donor availability issues improved significantly with umbilical cord methods and even more with haploidentical donor practice. So the remaining points in autologous transplantation were, later on, reduced early transplant-related mortality and some very high-risk biological condition patients.

Some factors that led to the dominance of allogeneic transplants following the initial wave of autotransplantation for leukemia are as follows:

a. Anyway, it became clear that autologous transplant mortality is significantly higher in leukemic patients compared to those with myeloma or lymphoma undergoing autologous transplantation. Autologous transplantation in acute leukaemia, depending on condition and

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modality, may carry a higher risk of early mortality, about 5-10%, than in myeloma or lymphoma [4].

b. So the age limit is higher, but frailty might also be an issue in autologous settings. In the meantime, mortality from early allogeneic transplantation has improved significantly [5,6].
c. Donor availability was a much more critical issue decades ago, but umbilical cord, haploidentical transplant, etc., provide much better donor finding possibilities [7]
d. Induction of GVL in autologous settings was not achieved (e.g., IL-2, cyclosporin A, etc.). However, some older methods, with improved technologies, have led to more recent efforts still aiming to achieve it [8–10]. More recently, magnetic sorting of CD96 cells, in vitro pulsing with an oncolytic virus, and, quite recently, the addition of a PD-1 blocker, as well as NK cell activation efforts, are promising approaches to achieve this goal. PD-1 blockade may enhance GVL and has been tried (pembrolizumab) for maintenance following autologous AML transplants. However, the many side effects of PD-1 ligand administration, including potential reductions or alterations in platelet counts and increased thrombotic risk, should also be considered when making decisions [11–13]. Nevertheless, more clinical experience is still needed to evaluate these approaches in real-life settings.
e. Purging of autologous stem cell graft in vivo by combining cytosin arabinosid with etoposide might also be an interesting approach. In vitro purging was not a reliable approach for many years. Interestingly, some recent efforts in high-tech screening are promising, even though they are far from clinical evaluation [14].
f. A potential drawback of autologous transplantation might be the development of clonal hemopoiesis, like in myeloma or lymphoma cases, along with myelodysplastic, etc. [15,16]
g. Autologous transplantation is not entirely free from thrombotic microangiopathy (TMA) and veno-occlusive disorders, but the incidence of these complications is considerably lower than in allogeneic settings. TMA is less frequent than in allogeneic contexts, except when high-dose platinum is used during conditioning treatment. Significantly fewer cases of VOD are reported following autologous transplant, probably <5% [5,14].
h. Iron overload (mainly in multitransfused myelodysplasia or myelofibrosis patients) hurts stem cell harvesting [17]
i. For the vast majority of patients, allogeneic transplantation, with its anti-leukaemic action, was and still is by far the best choice for cure or survival improvement. The autologous route was almost completely forgotten [14]

More Recent Concepts to Reevaluate Autologous Transplants in Leukemias

Over the past few years, due to the modernization of AML classification and new concepts regarding allo-transplant timing to achieve MRD negativity, the approach to autologous transplants in acute leukemias has been revisited. There is very strong evidence that, in acute leukemia, the timing of allogeneic transplantation is the most critical factor in attaining deep molecular remission (not only clinical or cytogenetic remission). A predictive model based on MRD burden has been developed, identifying a threshold of 0.05% MRD; patients with levels below this threshold have a significantly lower risk of relapse, with a 4.6-fold reduction in relative risk. This raises the question: how does leukemia autologous transplantation work? What are the results? If stem cell harvesting occurs during this profound MRD/molecular remission period, does it influence the relapse rate across different leukemia types and subsets [4,6,14] ?

Perhaps the indication for autologous transplantation is not limited to elderly, frail patients (or those without a donor) but also applies to certain other types or subsets of acute leukemias [18]. The availability of alternative stem cell sources, including most recently T-replete haploidentical marrow or peripheral blood, as well as the increasing use of reduced-intensity conditioning (RIC), makes allogeneic transplants feasible for nearly all patients with acute leukemia up to the age of 70. Autologous stem cell transplantation (ASCT) to consolidate complete remission (CR) offers an alternative in specific circumstances. Despite its association with a higher relapse rate, autologous

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transplantation offers benefits such as lower non-relapse mortality, hospitalisation time, absence of graft-versus-host disease (GVHD), and improved long-term quality of life. The recent use of intravenous busulfan (IVBU) combined with high-dose melphalan, along with enhanced monitoring of minimal residual disease (MRD) and maintenance therapy after autografting, has generated renewed interest [6,14,19].

On the other hand, several innovative purging strategies have been explored. One approach involves positive selection of normal hematopoietic stem cells using CD34 and/or CD133 markers. This method can be safely and effectively used in 50% of AML cases, as indicated by the absence or low expression of these markers at diagnosis, which remains stable at relapse. This technique achieves a 3-4 log reduction in tumour cells while maintaining a median recovery of 50% of normal stem cells. Otaroundher methods include ex vivo purging with oncolytic viruses such as myxoma virus (MYXV), which selectively eliminate cancerous stem and progenitor cells from AML patient samples while sparing normal CD34+ hematopoietic stem and progenitor cells capable of restoring haematopoiesis. Magnetic-activated cell sorting with antibodies targeting AML-specific antigens, such as CD96, has also shown promise, achieving over a 2-log depletion of target cells without impairing the viability or differentiation potential of healthy haematopoietic progenitor cells.

In vivo purging strategies, such as administering early intensification therapy with high-dose cytarabine and etoposide before stem cell collection, have demonstrated a significant reduction in relapse risk, with disease-free survival rates of 68.8% compared to 35.5% in patients not receiving this treatment. Additionally, combinations of cryopreservation, hyperthermia, and the ether lipid ET-18-OCH3 have been shown to achieve at least a 1-log depletion of AML blasts. Stem cell processing technologies, along with microbiome optimisation settings, and Wilms tumour gene 1 (WT-1) vaccination, have led to promising antileukaemic immunoreactivity, even in some autologous settings [12]. The choice of purging method often depends on the patient's specific disease characteristics, including MRD levels and antigen expression profiles and probably some microbiome modifications may also improve results [13,20,21].

Immunological interventions raise the hope of creating some GVL-like antileukemic effect with interferon, or induced stem cell origin NK cells [22,23].

Stem cell processing technologies may utilize new approaches to modify the immunoreactive cell composition of the harvested graft in ways that might promote antileukaemic immunoreactivity, even in some autologous settings [24].

So, considering all this, we aim to review the leukaemic conditions in which autologous transplantation must be the first step, or a powerful option like some well-defined leukaemic subgroups in which it might be slightly better than first-line allogeneic transplantation, and some other situations in which it should be considered a valuable alternative to allogeneic transplantation, especially with maintenance settings.

Provoking GVL following autologous transplantation, which had not been achieved for decades despite various, ultimately unsuccessful efforts, received renewed attention. A good example is the use of manoeuvres to activate NK cells, as well as the administration of PD-1 inhibitors in the post-transplant phase [13].

More recently, after better identification of patients in really complete molecular remission, some subgroups of acute leukemia patients were increasingly identified as benefiting equally or even slightly more with an autologous approach, opening doors for frailty patients, where transplantation modality could also be combined with maintenance modalities, and, in the end, the survival might be better or equivalent to allogeneic transplantation.). So, considering all this, we aim to review the leukaemic conditions in which autologous transplantation must be the first step, or a powerful option like some well-defined leukaemic subgroups in which it might be slightly better than first-line allogeneic transplantation, and some other situations in which it should be considered a valuable alternative to allogeneic transplantation, especially with maintenance settings. Innovative purging and GVL-provoking efforts may further shape allogeneic versus autologous transplant decisions, likely in the near future.

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Clinical areas and indications for autologous transplantation and leukemias

General considerations: There is virtually no theoretical upper age limit for autologous transplantation in acute leukemias. However, frailty can be independent of chronological age, which may limit indications.

Stem cell harvesting might also be necessary if allogeneic transplantation is the chosen treatment, and may serve as a bridging option in the event of graft failure to obtain a new donor and stem cells. Clearly, in some cases, if allogeneic transplantation is performed near the upper age/biological limit, relapse may be treated as an option among others with an autologous transplant.

Indications

Plasmacytic Leukemia, Autologous Transplantation

Plasmacytic leukemia is a strong indication for first-line autologous transplantation, practically a must. More recent data show that allo-transplant in this condition does not offer any benefit compared to autologous transplantation. Maintenance should follow the intervention tn the standard way [25–28].

Chronic Lymphocytic Leukemia (CLL)

Autologous transplantation in CLL carries a high mortality risk as opposed to myeloma or other lymphomas. There are powerful new medical treatments that attain deep remissions and improve survival, so it seems really outdated, except for very special, well-defined conditions, such as Richter transformation in CLL [29–31].

Acute Myeloid Leukemia (AML)

Few retrospective studies have compared outcomes following alternative donor versus autologous transplants for remission consolidation. Geno-identical and pheno-identical allogeneic stem cell transplantations are undisputed gold standards.

The availability of alternative stem cell sources, including, most recently, T-cell-replete haploidentical marrow or peripheral blood, along with the increasing use of reduced-intensity conditioning, makes allogeneic transplants feasible for nearly all patients with acute leukemia up to the age of 70. Autologous stem cell transplantation to consolidate complete remission provides, in certain cases, an alternative. However, although it is associated with a higher relapse rate, autologous transplantation features lower non-relapse mortality, no risk of graft-versus-host disease (GVHD), and an improved quality of life for long-term survivors.

Extensive studies have recently been conducted to identify well-defined subsets of AML patients who benefit from autologous transplants, with outcomes that are comparable or even slightly better. In these subgroup analyses, an important initial criterion is the presence of a deep, MRD-negative first remission.

There is still evidence that poor-prognosis AML transplant remains undoubtedly an allogeneic intervention [14]. So, mainly the intermediary prognostic category moved into the focus of revisiting allogeneic/versus autologous transplant modalities [14].

Favourable risk AML, both autologous and allogeneic, had a 5-year relapse-free survival rate in the 60% range [14,32,33]. In the intermediate, non-selected group, 5-year survival was about 20% higher, mainly due to a larger proportion of relapse (20% range) in autologous settings [34]. However, Yoons et al.'s data were also clear that in the intermediate prognostic group of AML, with favourable (or no) molecular alterations, the 5-year OS was 84%, which was better than with allogeneic transplantation [34].

Intermediate-risk cytogenetics with favourable molecular risk, whether using autologous or allogeneic procedures, was associated with similar overall survival: 62% versus 66%. This provides a

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valid, less toxic option [30,33]. As more data are collected or published, molecular subtypes of intermediate-risk AML may become potential candidates for autologous transplantation [30].

Intermediate-risk cases with good MRD (including RUNX- -RUNX1T1, i.e t8:21 quantitation, differential evaluation of IDH1 and IDH2 in MRD assessment) and no flt-1 mutation had results comparable to haplo allo patients, whereas haplo allo is better in intermediate-risk cases with flt-3 mutations. The role of anti-flt medications following auto is still unclear. The Pethema group published a large patient group analysis showing that patients with no cytogenetic alterations and no Flt-ITD mutation had better response rates and survival with autologous than allogeneic transplantation, and they consider autologous transplantation still an alternative for selected AML patients, achieving best results in MPN-1 mutated flt-3 ITD negative cases [35]. Other data also indicate that, in the intermediate prognostic group, AML autologous transplant patients with Flt3 wild-type fared better than those who received haploidentical allogeneic transplantation. However, Flt-3-positive cases had significantly worse outcomes with autologous transplants [36].

The Spanish multicenter trial compared 2 subgroups with intermediate-risk cytogenetics.

AML patients: a combined with favourable cytogenetics (mutated NPM1, CEBPA biallelic mutation) or with unfavourable molecular condition (NPM1 non-mutated, flt-3 ITD mutation). It became clear that the favourable molecular subgroup autologous result was comparable to allogeneic transplantation (5-year OS 77% versus 70%). Still, in the unfavourable molecular subgroup, 5-year OS was available for only 40% of patients; in this cohort, allogeneic remains the standard mode of transplantation [35].

Sula et al. in core-binding factor-positive AML cases had excellent results with the autologous approach, with CBF usually disrupted in 16/21, resulting in a relatively good prognosis even without transplant, but relapse remains an issue. In patients with FLT3 mutations, the haplo type confers better survival [36].

While allogeneic transplantation (using donor cells) remains the preferred option for high-risk patients, auto-HSCT is a valuable alternative for intermediate- or favourable-risk patients (molecular approach), especially when a matched donor is unavailable [37]. In cases of AML second relapse, the recommendation is repeated allogeneic transplantation, not autologous transplantation [38].

Maintenance therapy after autologous transplant has been studied, and the use of sorafenib has been clearly proven to be beneficial. Also, there are data on azacytidine and giltertinib use in flt3-positive cases. However, this data is the allogeneic setting, and has not been investigated after autologous transplantation. It is very likely that the us of maintenance should be incorporated into the treatment plan after autologous transplantation, as well[14,30,37].

Acute Promyelocytic Leukemia (APL)

Due to the effectiveness of first-line retinoic acid and arsenic-based therapies, bone marrow transplantation has a very limited role in treatment. Refractory or first-relapse cases should receive allogeneic transplantation (there is no role for autologous). Still, after a PML-RARA-negative PCR result, a stem cell graft might be used in patients with limited biological resources to prevent further relapse. However, new data are very promising, including a large retrospective analysis of 294 patients showing that autologous transplantation yields superior overall survival compared with allogeneic transplanted APL patients in second complete remission. Five-year OS was 75% for autologous versus 54% for allogeneic, primarily due to significantly lower treatment-related mortality i.e., 2% versus 30% [39]. These findings are part of extensive international guidelines (involving childhood), in a second relapse if stem cells were harvested during complete molecular remission. [40–44]

AML, In Summary

While allogeneic transplantation remains superior for high-risk patients, autologous transplantation is a valuable alternative for intermediate- or favourable-risk patients, especially when a matched donor is unavailable. It is generally not recommended for poor-risk cytogenetics. In well-

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defined subgroups, results are competitive with or better than those of allogeneic transplantation. Good-prognosis AML cases and intermediate-risk (without cytogenetic alterations) cases in first MRD-negative remission may benefit from allogeneic (haplo) transplants or achieve better outcomes. CBF and CEBPA results should also be considered in decision-making, as some data indicate efficiency in the 2nd CR as well [45]. Promyelocytic leukemia second relapse shows better results with an autologous transplant compared to an allogeneic one.

ALL

Autologous stem cell transplantation (ASCT) is rarely used as a primary treatment for adult acute lymphoblastic leukemia (ALL), especially in standard-risk patients, because it is less effective than conventional consolidation and maintenance chemotherapy. In the final results of the International ALL Trial (MRC UKALL XII/ECOG E2993) [47], patients assigned to autologous transplantation had a lower 5-year overall survival (OS) of 37% compared to 46% in those receiving chemotherapy [46]. The greatest survival benefit in standard-risk ALL is achieved with matched sibling allogeneic transplantation in first complete remission. There are many powerful innovations in ALL treatment standards, including specific immune and cell therapies. In summary, while autologous transplantation is not the preferred option for most adult ALL patients, it can serve as a viable alternative when a matched donor is unavailable, particularly in patients with favourable risk features and minimal residual disease negativity. The decision must weigh the higher relapse risk associated with autologous transplants against the increased transplant-related mortality linked to allogeneic transplants. Several recent multicentre trials have considered autologous transplantation a good option in the late phase of Philadelphia-negative Precursor T-Cell ALL [47]. Giebel et al. describe non-prospective data on autologous. transplantation in Philadelphia-negative ALL, over the age limit of 55 years, and concluding as an alternative approach with some benefit [48].

CML

Primary intention autologous transplantation is not indicated in CML (there are excellent drugs), chronic neurophilic leukemia, or atypical CML. Basically, CML, for the time being, is becoming less and less a transplant indication; if so, it should be allogeneic. Autologous transplantation might be extremely rare and, except for elderly and very frail patients, would usually result in shorter remission [49,50].

Discussion

Autologous transplantation in leukemia was a recommended option 20-30 years ago, mainly due to issues with donor availability, age restrictions, and biological conditions, along with better early post-transplant mortality rates. Over time, practices have evolved as new donor sources and haploidentical transplants have emerged, and early post-allogeneic mortality has improved, however early autologous mortality in leukemia still exceeds that in myeloma or lymphoma autografting. Undoubtedly, TMA and VOD are less common in autologous settings. Traditional approaches, such as in vivo or in vitro stem cell purging or the induction of anti-leukaemic immune responses, have long failed. It is also clear that secondary MDS and clonal haematopoiesis can occur after some or a few autotransplants, so it remained an option for quite old and frail patients. Otherwise, allogeneic transplants show clearly better results, with fewer relapses due to GVL.

This rather disappointing opinion started to change in some respects. New in vitro cell selection/pugging approaches have been developed (awaiting large trials). NK cell activation and administration of PD-1 inhibitors might elicit a more or less pronounced antileukemic immune response; we are still awaiting clinical proof.

Even more importantly, it is clear that some in special conditions mean an obligation to start with an autologous transplant, like plasma cell myeloma with plasma cell leukemia, or acute promyelocytic leukemia in 2nd relapse (if molecular remission graft is available) Even more

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importantly some subgroups of acute myeloid leukemia, mainly intermediary prognostic cases, and precursory T cell subset of ALL results are slightly better with the autologous approach. They should be screened later on clonal hemopoiesis and MDS, too.

Of course, the donor availability problems (if they are really present) and age/biological condition are still moving things toward autologous transplant.

Nevertheless, no data demonstrate the superiority of alternative allogeneic donor over autologous transplantation at the time of undetectable MRD in patients with good- and intermediate-1-risk acute myeloid leukemia (AML), especially with favourable molecular alterations, in first complete remission, and in acute promyelocytic leukemia in second complete remission.

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Abbreviations

The following abbreviations are used in this manuscript:

- Arhgef: Rho Guanine Exchange Factor, cytokine modification for GVL in transplant modalities
- AML: acute myeloid leukemia
- ALL: acute lymphoid leukemia
- APL: acute promyelocytic leukemia
- ASCT: autologous stem cell transplantation
- CBF: core binding factor
- CEBPA: CCAAT/enhancer-binding protein
- CLL: chronic lymphoid leukemia
- CML: chronic myeloid leukemia
- CR1, CR2: first, second complete remission
- ET-18-OHC3: edelfosine cell-permeable, reversible cytotoxic agent
- FLU: fludarabine
- GVHD: graft versus host disease
- GVL: graft versus leukemia effect
- IL-2: interleukin 2
- PD1-L: programmed cell death ligand 1
- IRn: irinothecan type treatment
- MDS: myelodysplastic syndrome
- MEL: meplhalane
- MRD: minimal residual disease
- OS: overall survival
- TBI: Total Body Irradiation
- TMA: thrombotic microangiopathy
- TRM: transplant-related mortality
- VOD (SOS): Veno-Occlusive Disease (VOD), also called Sinusoidal Obstruction Syndrome (SOS)
- WT-1: Wilms tumour gene 1

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