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Review

Extramedullary Escape in Acute Lymphoblastic Leukemia (ALL) After Allogeneic Transplantation: A Practical Guide to Diagnosis and Management

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Abstract

Extramedullary relapse (EMR) of acute lymphoblastic leukemia (ALL) after allogeneic hematopoietic stem cell transplantation (Allo-HSCT) represents a clinically and biologically distinct entity compared with medullary relapse, characterized by marked heterogeneity, compartmental immune escape mechanisms, and generally poor prognosis. EMR arises at the intersection of clonal resistance, evolutionary disease adaptation, and heterogeneous distribution of the graft-versus-leukemia effect, resulting in evolutionary trajectories that are often dissociated between medullary and extramedullary compartments. In the absence of prospectively validated therapeutic algorithms, EMR management requires a structured and adaptive approach based on multidimensional assessment integrating leukemia biology, disease burden and anatomical distribution, bone marrow minimal residual disease (MRD) status, and immune reconstitution. Therapeutic strategies include local treatments, targeted agents, immunotherapies, and immunomodulatory interventions, applied within a dynamic sequence tailored to treatment response. Follow-up plays a central role as an active tool for prognostic stratification and clinical decision-making, enabling early detection of systemic progression and optimization of the timing of consolidative strategies, including second Allo-HSCT in selected patients. An integrated and biologically driven management of post-Allo-HSCT EMR is essential to improve outcomes in this high-risk clinical setting.

Keywords: extramedullary relapse; acute lymphoblastic leukemia; allogeneic hematopoietic stem cell transplantation; immune escape

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1. Introduction

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy characterized by high biological aggressiveness and a significant risk of relapse, particularly in adult patients [1]. In this context, allogeneic hematopoietic stem cell transplantation (Allo-HSCT) represents a consolidated therapeutic strategy for high-risk patients, those with relapsed disease, or those refractory to conventional therapies, owing to the combined cytotoxic effect of the conditioning regimen and the immunological graft-versus-leukemia (GvL) effect [2]. Despite the advances achieved in recent years in donor selection, conditioning strategies, graft-versus-host disease (GvHD) prophylaxis, and measurable residual disease

(MRD) monitoring, post-transplant relapse remains the leading cause of therapeutic failure and long-term mortality [3].

Historically, relapse of ALL after Allo-HSCT has been considered predominantly a bone marrow event. However, increasing evidence indicates that a non-negligible proportion of patients develop extramedullary relapse (EMR), broadly defined as the reappearance of leukemic cells at sites outside the bone marrow, either in the absence of or with minimal detectable marrow involvement or in association with concomitant medullary relapse, although these conditions may reflect distinct biological mechanisms.

Available data suggest that EMR occurs in approximately 10–20% of adult patients with ALL after Allo-HSCT, although incidence may vary according to disease characteristics, transplant-related factors, and duration of follow-up.

For the purpose of this review, EMR refers to the reappearance of leukemic cells at sites outside the bone marrow.

EMR may occur as an isolated event or can precede a subsequent systemic relapse, suggesting pathogenetic mechanisms distinct from those underlying classical marrow relapse [4].

From a clinical standpoint, EMR is of particular relevance because of its prognostic impact and the challenges it poses in its management. Several retrospective studies have shown that EMR is associated with reduced overall survival (OS) and high rates of disease progression, in the absence of standardized therapeutic strategies based on prospective evidence [5]. Moreover, EMR raises important questions regarding the actual immunological control exerted by the GvL effect at extramedullary sites.

The diagnosis of EMR is often complex and delayed. Post-transplant follow-up is primarily focused on bone marrow assessment, with serial MRD monitoring by highly sensitive techniques such as multiparametric flow cytometry (MFC) or molecular assays [6]. In many cases of EMR, marrow MRD remains persistently negative, creating a discrepancy between apparent hematologic remission and occult extramedullary progression. In addition, symptoms are often nonspecific or organ-dependent and may mimic opportunistic infections, inflammatory manifestations, or immune-mediated complications such as GvHD, further delaying diagnosis.

From a biological perspective, extramedullary sites may act as true immunological and pharmacological "sanctuaries," characterized by reduced penetration of systemic drugs and less effective immune surveillance [7].

Recent literature has provided relevant contributions to the understanding of extramedullary disease in acute lymphoblastic leukemia. In particular, Cassaday (2025) and Agrawal et al. (2025) [8,9] have respectively explored the role of sanctuary sites in the era of immunotherapy and the biological and clinical features of extramedullary involvement, with a particular focus on B-cell ALL. However, these contributions do not specifically address the unique challenges of the post-transplant setting.

In this context, the present review aims to specifically examine extramedullary relapse after allogeneic hematopoietic stem cell transplantation, providing an integrated perspective that combines biological mechanisms, clinical manifestations, diagnostic challenges, and therapeutic strategies. Particular emphasis is placed on the interplay between the graft-versus-leukemia effect, immune escape mechanisms, and tissue-specific microenvironments, with the aim of outlining a practical and clinically oriented approach.

This favorable microenvironment may allow the persistence and expansion of resistant leukemic clones, underscoring that EMR should be considered a distinct clinical entity requiring a high index of suspicion, dedicated diagnostic tools, and integrated, personalized therapeutic strategies (Figure 1).

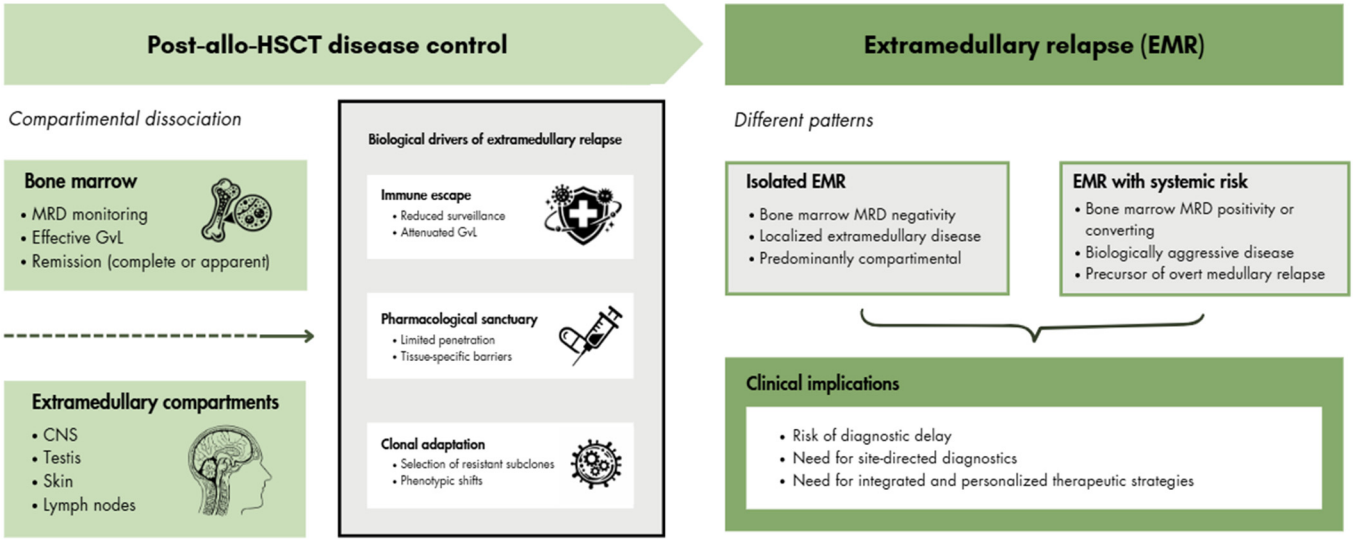


Figure 1. Biological and clinical patterns of extramedullary relapse after Allo-HSCT. Abbreviations: CNS, central nervous system; EMR, extramedullary relapse; GvL, graft-versus-leukaemia; MRD, minimal residual disease.

2. Mechanisms and Determinants of Extramedullary Escape in ALL After Allogeneic Transplantation

Extramedullary escape after Allo-HSCT results from a complex interaction between disease-specific biological features, host immunological conditions, and the anatomical characteristics of different tissue compartments [8]. Identification of the most frequently involved sites and the main associated risk factors is essential to understand the mechanisms underlying EMR and to design more targeted surveillance and clinical intervention strategies (Table 1) [10].

Table 1. Main sites of extramedullary relapse after Allo-HSCT.

Site	Typical Presentation	Key Diagnostic Approach	Differential Diagnosis
CNS	Neurological symptoms	MRI ± CSF (MFC)	Infections, cerebrovascular accidents; other CNS malignancies
Testis	Enlargement or pain	Ultrasound ± biopsy	Infections; other testicular tumors
Skin	Infiltrative or refractory lesions	Skin biopsy	Infections; adverse drug reactions: GvHD; other cutaneous tumors
Lymph nodes	Persistent lymphadenopathy	PET/CT ± biopsy	Infections; PTLD; inflammatory diseases
Bone/Soft tissue	Local pain or mass	MRI or PET/CT	Infections

Abbreviations: CNS, central nervous system; CSF, cerebral spinal fluid; CT, computerized tomography; GvHD graft-versus-host disease; MRI, magnetic resonance imaging; PET, positron emission tomography; PTLD, post-transplant lymphoproliferative disorders.

2.1. Organs Involved in Extramedullary Relapse

The anatomical distribution of EMR reflects differences in tissue pharmacokinetics of systemic treatments, trafficking and function of effector immune cells, and interactions between leukemic cells and the local microenvironment. In certain sites, these factors may result in suboptimal disease control despite complete marrow remission [9,11].

Beyond pharmacokinetic differences and the anatomical features of specific compartments, increasing attention has been directed toward the role of tissue-specific leukemic niches in the pathogenesis of extramedullary relapse [8,11]. These local microenvironments

should not be regarded as passive sites of disease localization, but rather as biologically active compartments capable of supporting leukemic cell survival and persistence through pro-survival signals and protection from allogeneic immune surveillance [8].

In particular, the dynamic interaction between leukemic cells, stromal and endothelial components, and tissue-resident immune cells contributes to the production of cytokines and chemokines that promote leukemic cell retention and clonal expansion within specific anatomical sites [8,11]. At the same time, the selective expression of adhesion molecules and chemokine receptors (such as CXCR4 and integrins) may facilitate leukemic cell trafficking and homing to permissive niches, favouring their stabilization in relatively protected compartments [8,12].

An additional key element is represented by the reduced infiltration and/or functional impairment of alloreactive T cells within these sites, resulting in a significant attenuation of the graft-versus-leukemia effect at the extramedullary level [7,8].

In addition, local immunoregulatory mechanisms, including the expression of immune checkpoint molecules and the presence of immunosuppressive cellular subsets, may further contribute to the establishment of an immune-privileged microenvironment.

This phenomenon, likely mediated by both physical barriers and local immunoregulatory mechanisms, contributes to the establishment of true "immunological sanctuaries" [7].

Taken together, these processes support a view of extramedullary relapse as the result of a complex interplay between leukemic cell biology and tissue-specific microenvironmental features, rather than a simple anatomical extension of medullary disease.

The central nervous system (CNS) represents the most frequently involved site in post-transplant EMR [9]. The blood–brain barrier affects the penetration and distribution of chemotherapeutic agents, rendering only a limited subset of systemic drugs effective, typically at high doses. Moreover, the cerebrospinal fluid compartment is characterized by quantitatively reduced and functionally modulated immune surveillance compared with the bone marrow, with fewer effector T cells and reduced cytotoxic activity, potentially resulting in the attenuation of the GvL effect. These factors contribute to the specific vulnerability of the CNS, where relapse may occur as an isolated event or precede systemic progression [12].

The testis represents another site at increased risk for EMR in ALL. The blood–testis barrier limits the exposure of leukemic cells to systemic drugs and immune effector cells. Consequently, testicular relapses may develop despite adequate marrow control and negative MRD. Clinically, these relapses may initially follow an indolent course, requiring careful evaluation during follow-up [13,14].

The skin is a relatively frequent site of extramedullary involvement. Clinical manifestations are heterogeneous and include nodules, infiltrative plaques, or erythematous–violaceous lesions [14–16]. Diagnosis may be challenging because leukemic skin involvement can overlap, both clinically and histologically, with opportunistic infections, drug reactions, or manifestations of GvHD [17].

Lymph nodes are frequently involved in EMR, particularly in the context of multifocal relapse. Persistent or progressive lymphadenopathy after Allo-HSCT should not be automatically interpreted as reactive or inflammatory but requires histological evaluation to distinguish leukemic relapse from other conditions, including infections and nodal GvHD [18]. This diagnostic requirement is particularly relevant in patients who presented with predominant nodal involvement at initial diagnosis, such as ALL with a lymphoblastic lymphoma–like presentation, in whom post-transplant relapse may preferentially occur within lymphatic compartments despite sustained marrow remission.

EMR has also been reported at less common sites such as the eye, breast, kidney, liver, gastrointestinal tract, bone, and soft tissues. Although rare, these localizations highlight the

ability of leukemic cells to adapt to heterogeneous tissue microenvironments and require an individualized diagnostic approach [19–21].

2.2. Clinical and Biological Risk Factors

Several clinical and biological factors have been associated with an increased risk of EMR after Allo-HSCT.

MRD is one of the main predictors of overall relapse: the presence of MRD positivity before or after transplantation is correlated with a significantly higher risk of relapse [22]. However, EMR may also occur in patients with persistently negative marrow MRD, highlighting a possible dissociation between disease control in the marrow compartment and in extramedullary sites [18,23,24].

From a biological perspective, T-lineage ALL shows a greater tendency to infiltrate extramedullary compartments such as the central nervous system, skin, and lymph nodes, often resulting in multifocal and clinically more aggressive relapse patterns [8,25].

The degree and duration of post-transplant immunosuppression are critical determinants of EMR risk. An intense or prolonged immunosuppression may attenuate the effectiveness of the GvL effect, favouring persistence of leukemic cells at extramedullary sites. In the same context, chronic GvHD, often considered an indirect marker of active GvL, has been associated with a reduced risk of marrow relapse; nonetheless, its protective effect appears less pronounced against EMR [10].

This apparent dissociation between the protective effect of chronic GvHD on marrow relapse and its limited impact on extramedullary relapse likely reflects a compartmentalization of the graft-versus-leukemia (GvL) effect across different anatomical sites [7,8,24]. In the bone marrow, leukemic cells are directly exposed to alloreactive T cells within a highly vascularized and immunologically active microenvironment, allowing effective immune surveillance. In contrast, extramedullary tissues may behave as relatively immune-privileged compartments, in which both physical and biological factors limit the efficacy of the allogeneic immune response.

A central mechanism underlying this phenomenon is the reduced trafficking and infiltration of T cells into extramedullary sites, resulting from alterations in chemokine gradients, adhesion molecules, and the presence of anatomical barriers such as the blood–brain and blood–testis barriers [12,13]. In addition, local microenvironmental conditions, including activation of immune checkpoint pathways and the presence of immunosuppressive cellular subsets, may further impair effector function.

This compartment-specific limitation of the GvL effect provides a biological explanation for the reduced protective impact of chronic GvHD against extramedullary relapse and has relevant therapeutic implications [7,8]. Strategies aimed at enhancing allogeneic immunity, such as donor lymphocyte infusion (DLI) or immunosuppression tapering, may be less effective at extramedullary sites due to impaired T-cell homing and local immune resistance mechanisms, supporting the need for integrated therapeutic approaches [4,7].

Transplant type and graft manipulation strategies may also influence EMR risk: alternative donor transplantation, ex vivo or in vivo lymphocyte depletion, and reduced-intensity conditioning regimens can alter the balance between immune control and relapse risk, potentially favouring extramedullary relapse patterns [26].

Taking these considerations into account, post-Allo-HSCT follow-up should integrate a systematic clinical evaluation with a focus on organs at risk. In patients with predisposing factors, selective and targeted use of instrumental investigations may allow earlier diagnosis of EMR and potentially improve clinical outcomes.

These clinical and biological factors likely interact with tissue-specific microenvironmental conditions, substantially contributing to the modulation of leukemic cell behavior and to the heterogeneity of extramedullary relapse patterns.

2.3. Lineage-Specific Differences in Extramedullary Relapse: T-Lineage vs. B-Lineage ALL

From both a biological and clinical perspective, the distinction between B-lineage and T-lineage ALL represents a fundamental determinant of extramedullary relapse (EMR) behavior after Allo-HSCT and should be systematically integrated into both disease interpretation and therapeutic decision-making [1,25].

T-lineage ALL is characterized by a higher intrinsic propensity for extramedullary dissemination compared with B-lineage disease [8,10]. This feature is likely related to enhanced tissue homing capacity, increased expression of adhesion molecules and chemokine receptors, and the presence of epithelial-to-mesenchymal transition (EMT)-like programs that confer greater cellular plasticity and migratory potential [8,12]. As a consequence, T-lineage ALL more frequently involves extramedullary compartments such as the central nervous system, lymph nodes, skin, and soft tissues, often presenting with multifocal and clinically aggressive patterns [9,10,17].

In addition to these biological features, T-lineage ALL appears to be less effectively controlled by the graft-versus-leukemia (GvL) effect at extramedullary sites, potentially due to differences in antigen presentation, immune recognition, and interaction with the tissue microenvironment [7,8]. This may contribute to a higher risk of compartmental immune escape and to the development of isolated EMR despite sustained marrow remission [8,11].

These differences have major therapeutic implications. In B-lineage ALL, the availability of targeted immunotherapies—including CD19- and CD22-directed agents such as blinatumomab, inotuzumab ozogamicin, and CAR-T cells—allows the integration of highly effective systemic strategies also in the setting of extramedullary disease. Conversely, in T-lineage ALL these options are not applicable due to the absence of target antigen expression [25].

As a result, the management of EMR in T-lineage ALL relies predominantly on alternative approaches, including intensive systemic chemotherapy, site-directed radiotherapy, and immunomodulatory strategies aimed at enhancing allogeneic immune control, such as immunosuppression tapering and donor lymphocyte infusion [3,4]. In this context, early consideration of consolidative strategies, including allogeneic transplantation when feasible, remains of central importance.

Emerging therapeutic strategies targeting T-lineage antigens (e.g., CD7, CD5, CD1a) are under investigation, although their clinical application is currently limited and largely restricted to experimental settings [1].

Overall, failure to clearly distinguish between B-lineage and T-lineage ALL in the context of EMR may lead to clinically relevant errors, particularly in the inappropriate use of lineage-specific immunotherapies and in the underestimation of the distinct biological behavior of T-lineage disease [1,11].

3. Diagnostic Approach to Extramedullary Relapse in ALL After Allo-HSCT

3.1. Clinical Suspicion and General Principles

The diagnosis of EMR in ALL after Allo-HSCT represents a critical issue in post-transplant management. Unlike medullary relapse, EMR frequently develops without evidence of disease in the hematopoietic compartment and may escape the traditional diagnostic paradigms which are primarily based on monitoring bone marrow MRD [27]. In this regard, a negative MRD should not be interpreted as a reassuring finding in the

presence of a suggestive clinical picture, as it does not exclude the presence of active disease at extramedullary sites [22,23].

Suspicion of EMR should be considered whenever new-onset or progressive organ-specific signs or symptoms appear in a patient in hematologic remission after Allo-HSCT. Neurological manifestations such as persistent headache, focal deficits, seizures, or cognitive alterations should raise suspicion of CNS involvement; changes in testicular volume, consistency, or pain require targeted diagnostic evaluation; infiltrative, atypical, or conventional therapy–refractory skin lesions should be considered potentially indicative of leukemic infiltration; persistent or progressive lymphadenopathy, in the absence of a clear infectious or inflammatory etiology, should raise suspicion of EMR [12,14,15,18].

The diagnosis of EMR requires the integrated use of radiological, cytological, immunophenotypic, and histological techniques, selected according to the suspected site of disease [4,26].

No single technique, when considered in isolation, is able to ensure an adequate diagnostic sensitivity in all clinical contexts; therefore, diagnostic accuracy depends on the appropriate indication for each examination and on its interpretation within the post-transplant clinical setting.

3.2. Imaging Techniques

Magnetic resonance imaging (MRI) represents the reference standard to evaluate the CNS The use of dedicated sequences with contrast medium allows the identification of leptomeningeal infiltrations, focal or diffuse parenchymal involvement, and meningeal thickening, even in the absence of cerebrospinal fluid positivity [28]. However, in the post-Allo-HSCT setting, MRI specificity is limited, as inflammatory lesions, infectious processes (particularly viral or fungal), and vascular complications may mimic leukemic infiltration on imaging. For this reason, radiological findings must always be interpreted in conjunction with clinical and laboratory data and, when possible, confirmed by direct sampling.

PET/CT may be useful for the identification of metabolically active extramedullary sites, particularly at nodal, cutaneous, osseous, or visceral levels, and is mainly indicated in cases of suspected multifocal EMR or in the presence of non-localizing systemic symptoms. However, the sensitivity and specificity of PET in EMR of ALL are not standardized and are inferior compared with other hematologic malignancies [29]. Additionally, inflammatory processes, opportunistic infections, and manifestations of GvHD may result in nonspecific increased uptake, limiting its definitive diagnostic value.

Conventional computed tomography (CT) maintains a complementary role, primarily in the initial evaluation of visceral masses or deep lymphadenopathy, but shows lower sensitivity compared with MRI and PET for the detection of early or diffuse infiltrations [30].

Overall, imaging techniques represent fundamental tools for the localization of suspected EMR sites, but rarely allow a definitive diagnosis in the absence of cytological or histological confirmation.

More recently, the integration of functional imaging with molecular disease assessment has led to the development of composite approaches such as PET-MRD, with the aim of providing a more comprehensive and biologically meaningful evaluation of disease burden [22,29]. Among its main advantages, this approach allows overcoming the compartmentalized view of the disease by integrating information on metabolically active extramedullary sites with bone marrow minimal residual disease data.

However, important limitations still remain: the lack of standardized criteria, the variability of uptake in inflammatory or infectious conditions, and the limited prospective validation in ALL all affect its interpretation and clinical applicability [29,30].

In the context of extramedullary relapse, PET-MRD represents a promising approach for an integrated assessment of response and risk of progression; however, its use should currently be considered exploratory and restricted to selected or research settings [30].

3.3. Cytological Evaluation and CSF Analysis

When a CNS EMR is suspected, lumbar puncture with cerebrospinal fluid (CSF) analysis remains an essential diagnostic step. Traditional CSF cytology, however, has limited sensitivity, particularly in the early phases of disease or in the presence of focal localizations not communicating with the CSF compartment. Integration with MFC significantly increases diagnostic sensitivity, allowing the identification of leukemic populations even at low frequency [31].

Negative CSF results do not definitively exclude CNS involvement, as disease detection may require serial repeated examinations. In the presence of a discrepancy between clinical presentation, imaging findings, and CSF data, diagnosis must be based on an integrated evaluation and a strong clinical suspicion could legitimize a therapeutic approach [32].

3.4. Tissue Biopsy and Biological Characterization

Biopsy of the suspected site, when technically feasible, represents the diagnostic gold standard for EMR. Direct sampling allows detailed histological evaluation and immunophenotypic analysis, enabling differentiation between leukemic relapse and infections, inflammatory reactions, or manifestations of GvHD [21,33,34].

Beyond confirming the leukemic nature of the lesion, direct sampling of the extramedullary tissue allows to assess whether the leukemic clone has undergone immunophenotypic changes compared with the initial disease. It may document loss or modification of target antigen expression, a phenomenon that represents a mechanism of selective immune escape following exposure to immunotherapies and may render subsequent treatments directed against the same target ineffective. When available, molecular analysis of biopsy tissue can further demonstrate clonal divergence and genetic evolution of the disease, supporting the concept that EMR may follow biological trajectories distinct from those of the bone marrow compartment [1,7,8,11].

In this context, liquid biopsy approaches based on the analysis of circulating tumor DNA (ctDNA) represent an emerging strategy for molecular disease monitoring [33]. Among its main advantages, ctDNA enables a minimally invasive and potentially dynamic assessment of clonal evolution, allowing the detection of relapse signals even in the absence of bone marrow involvement and partially overcoming the limitations of approaches based exclusively on bone marrow sampling.

However, the clinical application of ctDNA in acute lymphoblastic leukemia still presents relevant limitations: sensitivity may vary according to disease burden and the site of extramedullary involvement, particularly in so-called “sanctuary” compartments; moreover, the lack of methodological standardization and validated cut-offs currently limits its routine use [34].

In the clinical context of extramedullary relapse, ctDNA may be considered a complementary tool to conventional techniques, with potential utility particularly in longitudinal monitoring and early identification of systemic progression [33,34].

The main limitation of biopsy lies in its invasiveness and the limited accessibility of involved sites; nevertheless, when the procedure is clinically safe, the diagnostic benefit generally outweighs procedural risk and represents a decisive element for appropriate therapeutic planning [4,27,33].

4. Multimodal Therapeutic Approaches in Extramedullary Relapse of ALL After Allo-HSCT

EMR of ALL after Allo-HSCT poses therapeutic challenges distinct from those of medullary relapse. In the absence of standardized recommendations and prospective studies.

EMR management relies mainly on retrospective evidence, small case series, and expert opinion; therefore, all therapeutic considerations discussed below should be interpreted as based on low-level evidence. (Table 2) [35].

Table 2. Therapeutic strategies for extramedullary relapse after Allo-HSCT.

Strategy	Main Role	Strength	Limitations
Intrathecal chemotherapy	CNS disease control	High efficacy with low systemic toxicity	No systemic effect
Radiotherapy	Local disease control	Rapid symptom relief	No systemic effect
DLI	Immune consolidation	Enhances GvL effect	Risk of GvHD
Blinatumomab	Low burden EMR	Systemic activity	Limited in bulky disease
Inotuzumab	Cytoreduction	High response rate	Hepatic toxicity
CAR-T	Refractory EMR	Activity in sanctuary sites	Durability/toxicity issues
Second HSCT	Curative intent	Long term control	High treatment-related risk

Abbreviations: DLI, donor lymphocyte infusions; EMR; extramedullary relapse; GvL, graft-versus-leukemia; GvHD, graft-versus-host disease; HSCT hemopoietic stem cell transplant.

4.1. Radiotherapy

Evidence supporting the use of radiotherapy in this setting is mainly derived from retrospective studies and small case series.

Radiotherapy (RT) may represent an effective therapeutic strategy for local control of EMR.

In CNS, RT may be used as focal treatment for parenchymal lesions, as cranial irradiation, or as craniospinal irradiation, particularly in the presence of disease refractory to intrathecal therapy or multiple relapses [36]. Similarly, in the presence of testicular involvement, local RT may allow disease control in isolated or paucifocal relapses [37]. The main advantage of RT lies in the rapidity of response and high local efficacy, with immediate impact on symptom control. However, it does not exert a systemic effect and may not prevent progression or the appearance of new extramedullary localizations. Moreover, in post-Allo-HSCT patients, cumulative exposure to cytotoxic and radiation treatments may increase the risk of late toxicity, limiting extensive use [38].

4.2. Donor Lymphocyte Infusion

Evidence on the efficacy of DLI in extramedullary relapse is limited and largely based on retrospective experiences.

Donor lymphocyte infusion (DLI) represents a commonly used immunotherapeutic strategy with the purpose of enhancing the GvL effect in patients with post-transplant relapse. The biological rationale of DLI in EMR is based on the hypothesis that increased allogeneic immune activity may contribute to disease control even at extramedullary sites, although this effect appears less pronounced than in the medullary compartment [39].

The efficacy of DLI in EMR appears heterogeneous and depends on several factors, including disease burden, relapse site, time elapsed since Allo-HSCT, and the presence of GvHD. The best responses have been observed in patients with isolated EMR, in medullary

remission and without active GvHD, suggesting that DLI is more effective in a setting of minimal or subclinical disease [40].

The main limitation of DLI is the risk of acute and chronic GvHD, which may be severe and potentially fatal. Consequently, DLI is generally administered at escalating levels and is often combined with gradual reduction in immunosuppression.

4.3. Targeted Therapies and Immunotherapies

Data on targeted therapies and immunotherapies in extramedullary relapse are mostly derived from subgroup analyses, retrospective studies, and small case series.

The introduction of targeted therapies and immunotherapies has profoundly modified the therapeutic approach to relapsed/refractory ALL, extending available options also to the post-Allo-HSCT EMR setting.

Blinatumomab, a bispecific anti-CD19/CD3 antibody, has shown significant activity in controlling MRD and in relapsed ALL. Although specific experience in EMR is limited, responses have been reported at extramedullary sites, particularly in patients with low disease burden, as its efficacy appears significantly reduced in bulky extramedullary disease, where limited T-cell penetration and local microenvironmental factors may impair its activity. The risk of neurotoxicity requires careful monitoring, especially in patients with prior CNS involvement [41–43].

However, it should be emphasized that most of the available evidence is derived from small retrospective series and case reports, often including highly heterogeneous patient populations and clinical scenarios [41,43]. No prospective studies have specifically evaluated blinatumomab in the setting of post-Allo-HSCT extramedullary relapse, and current use in this context largely relies on extrapolation from data in relapsed/refractory ALL [42].

In addition, its mechanism of action, which depends on effective T-cell engagement and trafficking, may partially explain the reduced efficacy observed in bulky or poorly vascularized extramedullary sites [41].

Inotuzumab ozogamicin (InO), an anti-CD22 antibody conjugated to calicheamicin, may represent another effective option in relapsed B-lineage ALL. In the context of EMR, InO is often used as debulking therapy or as a bridge to second transplantation. The risk of hepatic toxicity, particularly veno-occlusive disease, is a critical issue in the post-transplant population [44,45].

Importantly, this risk is not only clinically relevant but also quantitatively increased in patients previously treated with Allo-HSCT compared with non-transplanted populations, as consistently observed across clinical experiences [44]. This aspect has major implications for treatment sequencing, particularly when inotuzumab is used as a bridge to a second transplantation, where cumulative endothelial toxicity may significantly increase transplant-related morbidity and mortality [44,45].

For this reason, careful patient selection and risk–benefit assessment are essential when considering inotuzumab ozogamicin in the post-Allo-HSCT setting.

Anti-CD19 CAR-T cells have shown potent antileukemic activity and represent a potential strategy also for EMR. Responses have been documented in various extramedullary sites, including the CNS, suggesting their ability to traffic to and persist in distinct anatomical compartments. In the post-Allo-HSCT setting, CAR-T cells are frequently considered as bridging therapy to a second transplant or, in selected cases, as an alternative to it. However, response durability, the risk of immune-mediated toxicity, and interactions with allogeneic immunity remain an area of active investigation [46,47].

A critical and often underemphasized issue is the use of CAR-T cell therapy in patients with active or recent GvHD. In this setting, the administration of CAR-T cells poses

significant clinical challenges, as the underlying inflammatory milieu and ongoing or recent immunosuppressive therapy may increase the risk of immune-mediated toxicities, including cytokine release syndrome and neurotoxicity, and may also impair CAR-T cell expansion and persistence [40].

Moreover, the choice between autologous and donor-derived CAR-T products in the post-Allo-HSCT setting introduces additional complexity, including regulatory constraints and the potential risk of exacerbating alloreactivity [40].

From an operational perspective, CAR-T cell therapy should be avoided or deferred in patients with uncontrolled active GvHD, in whom clinical stabilization should be prioritized before infusion. In patients with recent GvHD or ongoing immunosuppression, decision-making requires a dynamic and individualized assessment integrating disease urgency, toxicity risk, and likelihood of efficacy [40]. In this context, bridging strategies may provide a window to optimize the patient's immunological status, while careful modulation of immunosuppression and early, intensive monitoring of immune-related toxicities are key to minimizing severe complications.

Overall, CAR-T cell therapy in the post-Allo-HSCT setting should not be considered as a standalone intervention but rather as part of a sequential and adaptive therapeutic strategy, in which timing of infusion and the patient's immunological condition are critical determinants of clinical benefit.

Moreover, the development of CAR-T cell therapies in T-lineage ALL is complicated by the phenomenon of "fratricide," whereby CAR-T cells recognize antigens shared with normal T cells and eliminate each other. Consequently, the management of extramedullary relapse in T-lineage ALL relies on alternative approaches, including intensive systemic chemotherapy, site-directed radiotherapy, and enhancement of the graft-versus-leukemia effect through immunosuppression tapering or DLI, with early evaluation of consolidative strategies such as allogeneic transplantation when clinically feasible.

In particular, the development of CAR-T cell therapies targeting T-lineage antigens is challenged by the risk of fratricide and prolonged T-cell aplasia; gene-editing approaches aimed at eliminating target antigen expression or the T-cell receptor represent promising strategies, although they are still under clinical investigation [46,47].

Overall, the use of targeted agents in post-Allo-HSCT extramedullary relapse should be interpreted with caution, as evidence remains limited and largely indirect, requiring individualized clinical judgment [40,46,47].

4.4. Second Allogeneic Transplantation

Evidence supporting second Allo-HSCT in extramedullary relapse is based on retrospective studies and remains limited.

Second Allo-HSCT may represent the only potentially curative strategy for a substantial proportion of patients with post-Allo-HSCT EMR.

This aspect is particularly relevant in T-lineage ALL, in which the limited availability of targeted immunotherapies makes allogeneic transplantation a central component of the therapeutic pathway, both in earlier and subsequent lines of treatment.

The main indications generally include achievement of complete or deep remission after salvage therapy and absence of uncontrolled active GvHD. Obviously, standard transplant eligibility criteria must be met.

The choice of conditioning regimen must take into account cumulative toxicity and the need for adequate antileukemic activity. Reduced-intensity or modulated regimens are often preferred, particularly in patients with previous exposure to myeloablative conditioning. The role of donor change remains controversial and is not supported by definitive

evidence but may be considered in the presence of early relapse or suspected immune escape [48].

Despite advances in supportive strategies, the outcome of second transplantation in the EMR setting remains burdened by high transplant-related mortality and a significant risk of relapse. Nonetheless, second Allo-HSCT may offer a concrete possibility of long-term disease control [49].

5. Practical Management Algorithm for Extramedullary Relapse After Allogeneic Transplantation

Accordingly, the following algorithm should be interpreted as a conceptual and practical framework based on retrospective evidence and expert opinion, rather than a standardized or prospectively validated recommendation.

Although no prospectively validated therapeutic algorithms exist for EMR after Allo-HSCT, clinical experience supports the use of a structured approach integrating disease biology, anatomical distribution, immune status, and available therapeutic options (Figure 2) [4,8,10,27].

5.1. Initial Assessment: Biological and Clinical Stratification of EMR

A central element of the initial evaluation of EMR is bone marrow MRD assessment using standardized high-sensitivity techniques (MFC, PCR, NGS). MRD positivity reflects biologically aggressive systemic disease, whereas EMR with persistently negative MRD suggests a compartmental relapse driven by local immune escape mechanisms [22,50,51].

This distinction carries relevant prognostic and therapeutic implications.

Immunophenotypic characterization by multiparametric flow cytometry is essential to confirm expression of target antigens (e.g., CD19, CD22, CD20) and to detect possible changes from the phenotypic profile at onset or previous relapses. This aspect is particularly relevant in patients previously exposed to immunotherapies, in whom antigen loss or down-regulation represents a well-recognized resistance mechanism [6,7,22,41].

Biological evaluation should include molecular characterization by PCR and/or NGS, aimed at identifying genetic alterations with biological, prognostic, and therapeutic relevance. This includes the detection of fusion gene rearrangements (e.g., *BCR::ABL1*, *KMT2A*, *ETV6::RUNX1*, *TCF3::PBX1*), mutations involving proliferative and cell survival signaling pathways (*RAS*, *JAK/STAT*, *FLT3*), alterations in tumor suppressor and cell cycle regulatory genes (*TP53*, *CDKN2A/CDKN2B*, *IKZF1*), as well as abnormalities associated with immune escape mechanisms (e.g., *B2M* and *HLA* genes) [52,53].

When technically feasible, molecular analysis of biopsied extramedullary tissue adds relevant value, as it may reveal clonal evolution, selection of resistant subclones, or genetic divergence compared with the marrow clone.

Assessment of the patient's immunological status represents an additional fundamental decision-making axis, with particular attention to the presence and severity of acute or chronic GvHD, the ongoing immunosuppressive regimen (drug type, cumulative dose, duration), and, when available, quantitative and functional immunological characterization. This includes lymphocyte counts with T-cell ($CD4^+$, $CD8^+$), B-cell, and NK-cell subsets by flow cytometry and, in selected contexts, evaluation of immune reconstitution, with particular focus on the T-lymphocyte compartment through clonal diversity studies (TCR sequencing) [4,24,39,40].

These parameters allow estimation of the residual GvL potential and appraisal of the feasibility of immunomodulatory strategies such as immunosuppression tapering or DLI, while balancing the risk of immune-mediated toxicity [39,40]

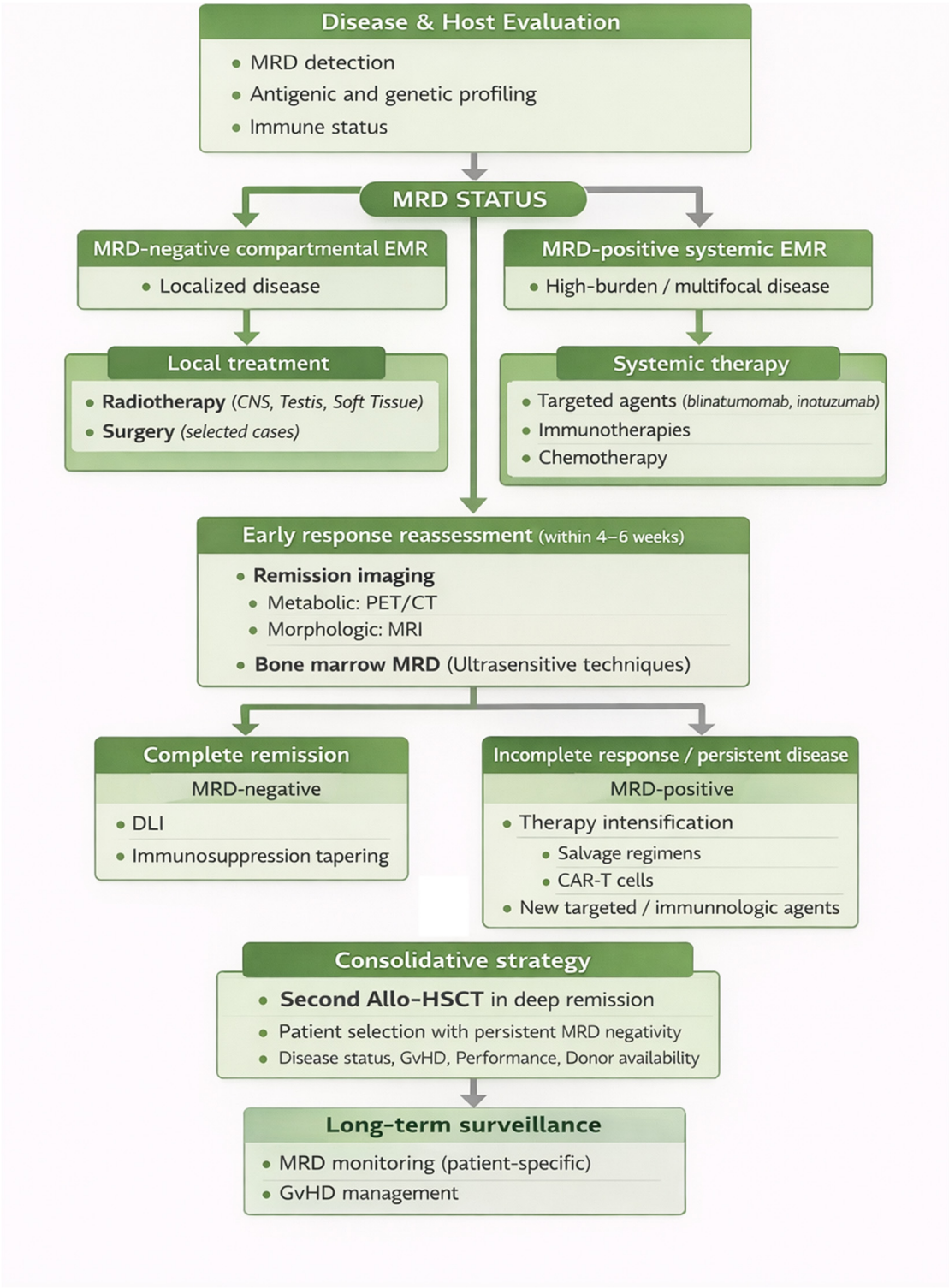


Figure 2. Practical therapeutic algorithm for the management of extramedullary relapse after Allo-HSCT. Abbreviations: CAR-T, Chimeric Antigen Receptor T-cell; CNS, central nervous system; DLI, donor lymphocyte infusion; GvHD, graft-vs-host disease; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; MRD, minimal residual relapse.

5.2. Initial Disease Control: Local Treatment and Early Cytoreduction

Initial treatment aims at rapid disease control and reduction in leukemic burden, according to relapse extent, site, and biological profile [4,7,11].

5.2.1. Local Treatment in Isolated or Paucifocal EMR

In patients with localized EMR and documented marrow remission, local treatment frequently represents the first-line strategy.

RT may be particularly considered in so-called "sanctuary" or immunologically protected sites, such as the CNS and the testis, and to a variable extent in selected soft tissue and bone localizations. In these settings, systemic treatment may be less effective due to pharmacokinetic limitations or a local microenvironment poorly permissive to the graft-versus-leukemia effect.

However, even in the presence of a complete local response, RT should be considered a disease control strategy rather than a definitive curative intervention [7,35–37].

The risk of disease progression despite initial control is particularly high in patients with unfavorable biological features, a history of multiple relapses, or prior exposure to selective immunological therapies [4,7,35].

Consequently, RT should be embedded within a multimodal strategy, in which local treatment serves as an initial step to reduce tumor burden, thereby facilitating the effectiveness of subsequent systemic or immunomodulatory therapies.

5.2.2. Early Systemic Approach in High-Burden or Multifocal Disease

In patients with multifocal EMR, high disease volume, or rapid clinico-radiological progression, initial treatment should be promptly oriented towards a systemic approach to achieve global cytoreduction and prevent evolution toward overt marrow relapse. The use of targeted therapies and immunotherapies allows overcoming the intrinsic limitations of exclusively local strategies, acting simultaneously on multiple clinically evident or subclinical disease sites. Bispecific antibodies such as blinatumomab may be particularly considered in patients with low or intermediate leukemic burden and marrow remission, whereas antibody–drug conjugates such as inotuzumab ozogamicin may be preferred in the presence of more spread or bulky disease, owing to their greater direct cytotoxic capacity [41,42,44,45].

Selection of systemic therapy must be strictly guided by immunophenotypic and molecular characterization of the disease, including target antigen expression (CD19, CD22, CD20), possibly lost after previous immunotherapy lines, and the presence of genetic alterations associated with resistance or aggressive biological behavior.

Additional decision-making elements include time elapsed since Allo-HSCT, cumulative exposure to prior therapies, and individual toxicity profile, with particular regard to hepatic and infectious risk [6,8,22,38,41].

In this context, RT may retain a complementary and selective role, directed toward dominant, symptomatic sites or those at imminent risk of functional compromise.

5.3. Enhancement of Allogeneic Immunity: DLI and Immunosuppression Modulation

After achieving initial control of extramedullary disease, the therapeutic algorithm should include the systematic evaluation of strategies to enhance the GvL effect, which represents one of the main determinants of long-term disease control after Allo-HSCT. In EMR, however, GvL effectiveness appears attenuated and strongly compartment-dependent, necessitating selective and rational use of immunomodulatory strategies [7,25,36,39].

DLI represents one of the main strategies to enhance the GvL effect and is most effective in patients with low disease burden, marrow remission, and absence of clinically significant GvHD. DLI may act as an immunological consolidative strategy, reducing the risk of systemic progression after a response achieved through local or systemic therapies.

This variable efficacy is consistent with the compartmentalized nature of the GvL effect, as discussed above, where limited T-cell trafficking and local immune resistance may reduce the activity of DLI at extramedullary sites.

From an operational standpoint, DLI is generally administered according to an escalating-dose schedule, carefully balancing between intensification of the GvL effect and the risk of immune-mediated toxicity. Timing of DLI relative to cytoreductive treatment is also crucial: infusion in the presence of high-volume active disease is associated with reduced efficacy and increased GvHD risk. Therefore, DLI finds its optimal placement after significant reduction in disease burden [7,25,39].

Immunosuppression modulation represents a complementary and often preliminary intervention to DLI. Gradual and controlled reduction in immunosuppression may allow partial reactivation of allogeneic immunity, sometimes sufficient to stabilize disease in selected patients. However, this strategy must be employed with extreme caution, as the risk of GvHD remains its principal complication [39].

5.4. Targeted Therapies and Immunotherapies as Adaptive Tools Within the Algorithm

Within the management algorithm for EMR after Allo-HSCT, targeted therapies and immunotherapies should be considered adaptive tools, with their application tailored to disease biology, tumor burden, relapse site, and therapeutic objective at a given phase of the clinical course [41,42,44,45].

Blinatumomab may find its optimal placement in the early phases of the algorithm in the presence of low disease burden, paucifocal EMR, or association with positive marrow MRD. The rationale for its use lies in its ability to induce deep immune-mediated cytoreduction, promoting recovery of immunological control and creating conditions for subsequent consolidation. However, its efficacy is limited in bulky extramedullary localizations, where access of effector T cells may be suboptimal.

Inotuzumab ozogamicin may play a distinct role within the algorithm, being primarily employed as a targeted cytotoxic debulking tool. Its high antileukemic activity makes it particularly useful in patients with high-burden, multifocal, or rapidly progressive EMR, in whom rapid reduction in tumor mass is required. In this sense, Inotuzumab is more frequently positioned as a bridge to a consolidative strategy rather than as definitive treatment. Therefore, its use must be prospectively planned, considering the cumulative risk of hepatic toxicity and veno-occlusive disease, especially in patients who are candidates for second Allo-HSCT [44,45].

Anti-CD19 CAR-T cells may be considered in cases of refractory, multiple, or relapsed EMR after conventional targeted therapies. Interest in their use in EMR derives from demonstrated trafficking capacity and antileukemic activity in extramedullary sites, including the CNS. Within the post-Allo-HSCT algorithm, CAR-T cells are predominantly used as salvage therapy or as a bridge to second transplantation, with the objective of achieving deep remission in patients otherwise not eligible for curative strategies. Overall, targeted therapies and immunotherapies allow a dynamic personalization of EMR treatment, adapting intensity and mechanism of action to the biological profile of the disease and the phase of the therapeutic algorithm. The conceptual basis for their use is not to replace allogeneic immunological strategies, but to create optimal biological conditions to maximize their efficacy and reduce the risk of systemic progression [7,11,39].

5.5. Dynamic Response Reassessment and Orientation of Consolidative Strategies

In the context of EMR of ALL after Allo-HSCT, reassessment of therapeutic response should be considered a structured longitudinal process, based on standardized clinical, radi-

ological, and biological parameters, aimed not only at documenting response but primarily at dynamic risk stratification and orientation of subsequent therapeutic decisions [4,10].

5.5.1. Decision-Making Value of Early Response Reassessment

An early reassessment, generally performed within 4–6 weeks from treatment initiation (whether local, systemic, or combined), is generally considered essential to determine its effectiveness and to identify early signals of biological resistance or subclinical systemic progression. This evaluation should integrate: morphological and/or functional imaging, selected according to the site of involvement (MRI for parenchymal or CNS sites; PET/CT for metabolically active localizations), to quantify local response and detect new extramedullary disease sites [28,29]; assessment of marrow MRD using high-sensitivity techniques (multiparametric MFC, allele-specific PCR, or NGS), which represents the main surrogate of systemic progression risk [22,51].

In patients who achieve complete radiological response at the extramedullary site associated with persistently negative marrow MRD, it may be appropriate to consider immunological consolidative strategies such as controlled immunosuppression tapering or donor lymphocyte infusion in the absence of active GvHD. In this subgroup, the objective is to amplify the GvL effect to reduce the risk of subsequent relapse [4,10,39,40].

Conversely, partial response, persistence of metabolically active extramedullary disease, or conversion to MRD positivity identify patients at high biological risk, in whom prompt modification of therapeutic strategy is indicated, including intensification or change of systemic therapy, integration of additional local interventions, or early evaluation of advanced salvage options.

5.5.2. Serial Reassessment and Definition of Consolidative Strategy

Subsequent reassessment, conducted serially after each relevant therapeutic intervention, primarily aims to define depth and stability of response, which are key elements for identifying patients eligible for high-impact consolidative strategies. In this setting, complete or deep remission should be stringently defined as the absence of radiological evidence of extramedullary disease associated with marrow MRD negativity documented by ultra-high-sensitivity techniques [4,6,22,51].

In this context, second Allo-HSCT is generally considered the only potentially curative option. However, high treatment-related mortality and risk of cumulative toxicity mandate rigorous candidate selection. The decision to proceed should be based on integrated assessment including disease biology, response achieved, GvHD history, immunological status, and overall clinical condition [48,50,52,53].

Timing of second Allo-HSCT is a critical determinant of outcome: benefit is significantly reduced in the presence of active or rapid progressive disease, whereas it is most significant in patients in deep, biologically controlled remission.

This approach maximises long-term EMR control probability after Allo-HSCT minimizing unnecessary exposure to highly toxic treatments [48,50].

5.6. Integration of the Decision-Making Algorithm into Clinical Practice

Taken together, the therapeutic strategies discussed can be integrated into an adaptive decision-making algorithm designed to address the marked biological and clinical heterogeneity of EMR of ALL after Allo-HSCT. Disease control through local or systemic strategies must not be considered in isolation, but rather embedded within a broader therapeutic pathway in which initial control represents the prerequisite for subsequent immunological consolidation or therapeutic intensification strategies represented by target therapies or immunotherapies [4,7,10].

Serial response reassessment enables prompt redefinition of therapeutic strategy, avoiding both prolonged exposure to ineffective treatments and delays in access to potentially curative options.

In patients who achieve complete or deep remission, documented by absence of radiological evidence of EMR and MRD negativity assessed by high-sensitivity techniques, second Allo-HSCT is generally considered the only potentially curative strategy. The decision to proceed with this intervention should be embedded within the algorithm as the outcome of a structured evaluative process that considers expected benefit in relation to disease biology, response achieved, and cumulative toxicity [48,49].

In the absence of standardized recommendations and dedicated prospective evidence, adoption of a structured decision-making algorithm based on biological, clinical, and immunological parameters represents an essential tool to translate the complexity of EMR into rational, personalized therapeutic choices with the potential to improve outcomes in this high-risk setting [4,7].

5.7. Limitations of the Algorithm and Integration of Non-Sequential Pathways and Supportive Care Strategies

It is important to emphasize that the proposed algorithm represents a decision-making framework primarily applicable to patients who are potentially eligible for sequential therapeutic strategies, with adequate organ function and sufficient performance status to tolerate multiple active treatment lines. However, in real-world clinical practice, a substantial proportion of patients with post-Allo-HSCT extramedullary relapse cannot be managed according to a standardized sequential therapeutic pathway.

In these patients, the clinical course is frequently influenced by factors that preclude the application of a stepwise therapeutic strategy, including cumulative toxicity from previous treatment lines and transplantation, progressive deterioration of general clinical condition, organ dysfunction, and decline in performance status. An additional critical determinant is disease biological evolution, including loss or downregulation of target antigens (e.g., CD19, CD22), which may limit or completely preclude the use of targeted immunotherapeutic approaches.

In this context, the therapeutic pathway should be interpreted as non-linear and clinically branched, with potential early deviations from the standard sequence of interventions outlined in the algorithm. The clinical objective is therefore no longer defined exclusively by progression through all available therapeutic steps, but rather by individualized treatment selection based on the balance between expected benefit, toxicity, and realistic probability of disease control.

In particular, in patients who are not candidates for further active therapies or who present with refractory disease associated with poor performance status, early integration of palliative and supportive care strategies should be considered an integral component of the overall management pathway. Palliative care in this setting should not be regarded as an end-of-life intervention, but rather as an active, multidimensional approach aimed at symptom control, functional and psychological support, and improvement of quality of life, potentially in combination with selected antileukemic interventions when appropriate.

6. Prognosis and Follow-Up in Extramedullary Relapse After Allo-HSCT—General Framework

Traditional prognostic models, predominantly based on hematologic parameters and marrow response, are often insufficient to capture the complexity of disease evolution in EMR [8,10].

Post-Allo-HSCT EMR lies at the intersection of clonal resistance, compartmental immune evasion, and altered distribution of the GvL effect, resulting in heterogeneous and sometimes dissociated evolutionary trajectories between the medullary and extramedullary compartments. Consequently, prognosis cannot be defined exclusively at the time of relapse but must be dynamically reinterpreted in light of therapeutic response and biological evolution over time [8,10,54].

6.1. Prognostic Implications and Biological-Clinical Determinants

EMR of ALL after Allo-HSCT is associated with an unfavorable prognosis, with overall survival rates inferior to those observed in isolated medullary relapses in major retrospective series [10].

The timing of relapse relative to Allo-HSCT constitutes one of the most robust prognostic determinants. Early relapses, generally defined as occurring within the first 6–12 months after transplantation, frequently reflect intrinsically resistant disease, characterized by early clonal instability and rapid loss of the GvL effect. In this context, EMR often represents the first clinical manifestation of a systemic failure of immunological control and is associated with limited response to salvage therapies and reduced eligibility for high-impact consolidative strategies. Conversely, late relapses tend to reflect mechanisms of progressive compartmental immune escape, in which selective pressure exerted by allogeneic immunity favors the survival of subclones capable of proliferating within partially protected anatomical niches. In these cases, the disease may retain greater sensitivity to targeted therapeutic interventions and immunomodulatory strategies [52,53].

Anatomical distribution and extramedullary disease burden significantly influence outcome. Localized or paucifocal forms, particularly when associated with documented medullary remission, show a higher probability of durable control, especially when incorporated into a multimodal strategy integrating local treatment, immunotherapy, and immunological consolidation. In contrast, multifocality, simultaneous involvement of multiple extramedullary compartments, or rapid progression identify biologically aggressive disease, often associated with subclinical dissemination and a reduced likelihood of sustained response [10,11].

Bone marrow MRD retains a central prognostic value even in the presence of apparently isolated EMR. Persistence or re-emergence of MRD positivity identifies a subgroup of very high-risk patients, in whom EMR likely represents an early manifestation of an evolving systemic relapse. Conversely, the observation of EMR in the context of persistently negative MRD suggests the existence of alternative evolutionary trajectories, characterized by clonal divergence and predominance of local immune evasion mechanisms, with distinct prognostic and therapeutic implications [10,51].

Finally, the molecular biology of relapse plays a decisive role in prognostic stratification. The emergence of high-risk genetic alterations, selection of resistant subclones, and acquisition of immune resistance mechanisms (such as antigen loss or alterations in antigen presentation pathways) directly influence both the likelihood of response to targeted and cellular therapies and the duration of disease control.

6.2. Post-Treatment Follow-Up: Integrated and Risk-Adapted Monitoring

In the setting of EMR after Allo-HSCT, follow-up should be conceived as a structured, longitudinal, and risk-adapted process aimed at early identification of therapeutic failure and dynamic redefinition of the clinical strategy.

Serial monitoring of bone marrow MRD using high-sensitivity techniques represents an indispensable pillar of follow-up, regardless of the initial site of relapse. In fact, MRD dynamics carry greater prognostic value than a single time-point measurement: a progressive

increase in MRD levels frequently precedes clinical progression and allows identification of phases of systemic reactivation that remain amenable to intervention; in contrast, persistently negative MRD confirmed over time identifies a subgroup of patients with more stable biological control, in whom the immediate risk of systemic dissemination is reduced [6,51].

Targeted radiologic follow-up plays a particularly relevant role in EMR, as extramedullary progression may occur silently, in the absence of hematologic abnormalities or re-emergence of bone marrow MRD. Imaging use should be guided by the initial disease site, individual risk profile, and administered treatment, prioritizing modalities that are reproducible and sensitive to residual disease. A selective and rational approach allows balancing diagnostic accuracy with clinical sustainability, avoiding both excessive surveillance and the risk of delayed diagnosis of compartmental progression [28].

Assessment of lymphocyte reconstitution, immunosuppressive status, and the presence of GvHD allows estimation of the residual potential of the GvL effect and guides subsequent therapeutic decisions [6,24].

Systematic integration of clinical, radiologic, biological, and immunological data enables continuous risk reassessment and is particularly relevant in a setting characterized by narrow therapeutic windows and salvage options associated with high toxicity [4,6,10].

6.2.1. Risk-Adapted Radiological Follow-Up

Radiological monitoring should be tailored to the initial site of extramedullary involvement, disease burden at relapse, and depth and durability of response.

In patients with isolated CNS EMR in complete remission, magnetic resonance imaging (MRI) of the brain and/or spine is generally recommended every 8–12 weeks during the first 6–12 months, reflecting the period of highest risk of early compartmental relapse. In case of sustained radiological and clinical stability, the interval may be progressively extended to 3–6 months, and subsequently to 6–12 months in long-term remission, in the absence of neurological symptoms.

In patients with isolated non-CNS extramedullary disease (including lymph nodes, skin, testis, or soft tissue), site-directed imaging or PET/CT (when appropriate) should be performed every 3–4 months during the early follow-up phase, with subsequent extension to 6 months in cases of sustained remission [28,29].

In patients with multifocal EMR, high disease burden at relapse, or suboptimal response to initial therapy, imaging should be performed more frequently, generally every 6–8 weeks in the initial post-treatment phase, until clear evidence of disease stabilization is achieved. Thereafter, surveillance intervals should be individualized according to biological response and risk profile.

In all settings, imaging should be anticipated in the presence of new clinical, radiological, or biological suspicion of relapse.

6.2.2. Bone Marrow MRD Monitoring

Bone marrow measurable residual disease (MRD) assessment remains a central component of post-EMR surveillance, even in cases of apparently isolated extramedullary disease.

During the early post-treatment phase (first 3–6 months), MRD evaluation using multiparametric flow cytometry, PCR, or next-generation sequencing should be performed every 4–6 weeks, particularly after completion of active therapy or during consolidation, when the risk of systemic reactivation is highest [6,22].

In the intermediate follow-up phase (6–24 months), in patients achieving disease control, MRD monitoring can be spaced to every 2–3 months, with shorter intervals reserved for high-risk biological profiles (e.g., T-lineage ALL, prior MRD positivity, or multifocal disease).

In long-term stable remission, MRD assessment may be further reduced to every 3–6 months, provided that no clinical, radiological, or immunological signs of disease recurrence are observed.

Importantly, any consistent upward trend in MRD, even below conventional positivity thresholds, should be interpreted as an early indicator of systemic reactivation and should prompt immediate therapeutic reassessment [51].

6.2.3. Risk-Adapted Follow-Up Strategy

Overall follow-up intensity should be adapted according to integrated risk stratification incorporating disease burden, biological features, response depth, and immune status.

Low-risk patients (isolated EMR, complete response, sustained MRD negativity, preserved immune reconstitution): progressive reduction in imaging and MRD frequency after consolidation, with transition to extended-interval surveillance.

Intermediate-risk patients (recent EMR, partial response, adverse biological features, or incomplete immune recovery): structured surveillance with intermediate imaging and MRD intervals, maintaining close longitudinal monitoring.

High-risk patients (multifocal disease, MRD positivity, early relapse after Allo-HSCT, or high disease burden): intensive surveillance with short imaging and MRD intervals, particularly during the first post-treatment months.

This risk-adapted framework allows balancing early detection of relapse with clinical feasibility, minimizing both under-monitoring and unnecessary over-surveillance.

Overall, the proposed intervals should be interpreted as general guidance rather than rigid rules and must be adapted to individual disease evolution and institutional practice.

7. Conclusions and Future Perspectives

EMR of ALL after Allo-HSCT represents a distinct clinical and biological paradigm compared with medullary relapse, characterized by a complex interaction between therapeutic selective pressure, clonal adaptation, and compartmental dysfunction of allogeneic immunity [4,5,8].

In particular, the distinction between B-lineage and T-lineage ALL represents a crucial element for the biological interpretation and clinical management of EMR, significantly influencing both patterns of extramedullary dissemination and available therapeutic options.

In this framework, the present review aims to provide a clinically oriented synthesis of current knowledge, integrating biological mechanisms of immune escape, site-specific disease behavior, and available therapeutic strategies into a unified interpretative model.

However, evidence accumulated in recent years indicates that EMR represents the expression of heterogeneous evolutionary trajectories, some of which may be amenable to durable control if intercepted early and managed with integrated therapeutic strategies [52,53]. Therefore, recognition of the current limitations of clinical practice and identification of new directions for development are fundamental elements for improving outcomes in this high-risk population.

7.1. Major Challenges and Gaps in the Clinical and Biological Management of Post-Allo-HSCT EMR

One of the major critical issues in the management of post-transplant EMR is the lack of a unified conceptual framework capable of coherently integrating the clinical, biological, and immunological dimensions of relapse. From a biological standpoint, EMR is frequently associated with the following:

Advanced clonal heterogeneity, with selection of subclones endowed with specific migratory and survival capacities within extramedullary niches;

Remodeling of the tissue microenvironment, which may promote protection of the leukemic clone through pro-survival and immunosuppressive signals;

Reduced effectiveness of the GvL effect outside the medullary compartment, likely related to limited infiltration of allogeneic T cells or local immune checkpoint activation mechanisms [6,51,52].

A deeper understanding of tissue-specific leukemic niches and of the dynamics of immune cell trafficking and function across different compartments represents a crucial step toward elucidating the mechanisms underlying immune escape in extramedullary relapse.

However, the lack of standardized tools for biological characterization of EMR limits the ability to accurately stratify patients and predict clinical course.

From a clinical perspective, an additional relevant gap is represented by the absence of shared criteria for assessment of extramedullary therapeutic response [28,30,32]. Unlike bone marrow MRD, which is supported by validated quantitative cut-offs, extramedullary response is generally defined using heterogeneous radiologic criteria that are often not comparable across studies. This methodological limitation has a direct impact on therapeutic decisions, particularly regarding selection and timing of high-risk consolidative strategies.

7.2. Emerging Strategies: Toward Biologically Guided Integration of Therapeutic Options

The evolution of post-Allo-HSCT EMR treatment is progressively converging toward an integrated therapeutic model that overcomes the traditional dichotomy between local and systemic interventions.

Targeted therapies and immunotherapies have assumed a central role offering the possibility to selectively modulate leukemic burden and partially restore immunological control [41,42,44].

CAR-T cell therapies represent one of the most relevant developments and have demonstrated significant activity even in patients with extensive extramedullary involvement [46,47]. Their mechanism of action, independent of HLA-mediated antigen presentation, renders them particularly attractive in the post-transplant setting. However, their optimal positioning within the therapeutic algorithm remains under debate, particularly with respect to:

- Durability of extramedullary response;
- Risk of antigen-negative relapse;
- Role as definitive therapy versus bridge to second Allo-HSCT.

In parallel, innovative tools for biological monitoring are emerging. Liquid biopsy, through analysis of circulating tumor DNA, allows to track clonal evolution in real time, overcoming intrinsic limitations of bone marrow sampling.

In a complementary manner, integration of advanced functional imaging (PET/CT) with bone marrow MRD assessment has led to the proposal of composite endpoints, such as the concept of PET-MRD, aimed at providing a global and biologically meaningful evaluation of therapeutic response. These tools may represent a decisive step toward truly multidimensional prognostic stratification [6,31,51].

7.3. Future Perspectives: Redefining Prognosis and the Decision-Making Algorithm

In light of current evidence, the need to abandon a static view of prognosis in post-Allo-HSCT EMR clearly emerges.

From a research perspective, development of dedicated prospective studies, harmonization of response criteria, and systematic integration of molecular and immunological biomarkers represent essential priorities.

Looking forward, the goal is to improve overall survival and transform EMR management from reactive to proactive, anticipating biological disease evolution and personalizing

therapeutic strategies based on dynamic and integrated parameters. Only through this paradigm shift will it be possible to significantly improve outcomes in one of the most complex and high-risk populations in transplant hematology.

To our knowledge, a structured and clinically applicable algorithm specifically focused on EMR after Allo-HSCT is still lacking, and this review aims to address this unmet need.

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