Cancer Immunology Connect
ISSN: 3105-3629
2025, Article ID. 2024.0002, Cite as: https://doi.org/10.69709/CIConnect.2024.193713

SCIFINITI

Review Article

OPEN ACCESS

Chronic Myelomonocytic Leukemia Relapse After Transplant

Fakhra Alafeefi[✉,1] **Afsheen Raza**[✉,1,*]

[1] Department of Biomedical Sciences, Abu Dhabi University, Abu Dhabi, United Arab Emirates

Article History
Submitted: October 05, 2024 Accepted: December 20, 2024 Published: January 08, 2025

Abstract
Relapse of Chronic Myelomonocytic Leukemia after allogeneic hematopoietic stem cell transplantation remains a significant challenge, with relapse rates reaching up to 50%, contributing to poor survival outcomes. This paper explores the factors influencing relapse, including disease biology and persistence of residual disease. Current, post- transplant strategies, such as maintenance therapies and immunomodulatory treatments, are discussed for their potential to reduce the likelihood of relapse. It also highlights emerging therapies, such as CAR-T cell therapy, targeted therapies, epigenetic modulators, and innovative combinations being tested in clinical trials. The aim of the paper is to provide a comprehensive overview of existing and future approaches to improve patient outcomes by addressing relapse prevention in Chronic Myelomonocytic Leukemia following transplantation.

Keywords:
Chronic myelomonocytic leukemia (CMML); relapse after transplant; allogeneic HSCT; CAR-T cell therapy; Myelodys- plastic syndromes (MDS); Myeloproliferative neoplasms (MPN)

1. Introduction

Chronic Myelomonocytic Leukemia (CMML) is a complex hematological malignancy characterized by the clonal proliferation of hematopoietic stem and progenitor cells. It is clinically defined by bone marrow dysplasia and sustained peripheral blood monocytosis, with a monocyte count $\geq 1 \times 10^9$/L persisting for over three months as shown in Figure 1a [1–3]. Historically, CMML was defined using this threshold; however, the 5th edition of the World Health Organization Classification of Hematolymphoid Tumors and the International Consensus Classification of 2022 introduced significant changes to the definition. These updates lowered the absolute monocyte count threshold to $\geq 0.5 \times 10^9$/L, incorporated oligomonocytic CMML into the diagnosis, and emphasized recurrent molecular aberrations over purely clinical criteria. Additionally, the CMML-0 subgroup was eliminated due to limited clinical relevance [1,3]. CMML predominantly affects older adults, with a median age at diagnosis of approximately 73–75 years, and shows a male predominance with a ratio of 1.5–3:1. The exact incidence of CMML is unknown but is estimated to be about four cases per 100,000 persons per year. Clinically, CMML is divided into two subtypes: myelodysplastic and myeloproliferative. This classification is based on the white blood cell count, with myeloproliferative CMML defined by a leukocyte count of $\geq 13 \times 10^9$/L [3]. These subtypes are clinically significant as they influence both prognosis and therapeutic strategies. In addition, around 15%–20% of cases will progress into AML within 3–5 years, which proves the condition's serious risks [3]. Genetic and molecular factors also play an important role in CMML. Recent studies have greatly enriched the understanding of the association between genetic abnormalities and CMML pathogenesis, which is helpful for risk stratification as well as accurate prognostic models for patients with CMML [4]. The primary treatments for CMML include hypomethylating agents (HMAs), targeted therapies, allogeneic hematopoietic stem cell transplantation (Allo-HSCT), and other options. Among these, allo-HSCT stands out as the only treatment with the potential to cure offering a 30% to

* **Corresponding Author:**
Afsheen Raza, Associate Professor of Molecular Biology, Department of Biomedical Sciences, Abu Dhabi University, Abu Dhabi, United Arab Emirates, raza.afsheen@adu.ac.ae

© 2025 Copyright by the Authors.
Licensed as an open access article using a CC BY 4.0 license.

2025, Vol. 1, Article ID. 2024.0002
https://doi.org/10.69709/CIConnect.2024.193713

40% five-year survival rate. Yet, high relapse rates 30% to 50% and non-relapse mortality 20% to 40% present major challenges, highlighting the need to improve strategies to lower relapse risk and improve survival outcomes [5]. This review looks into other approaches to manage CMML relapse after allo-HSCT tackling issues in choosing patients, donor matching, conditioning regimens, and preventing GvHD. It stresses the importance of stopping relapse as a key challenge in CMML treatment and improving survival with innovative management approaches. Also, it covers diagnostic criteria, prognostic scoring systems, recent advances in treatment based on new studies and updated guidelines.

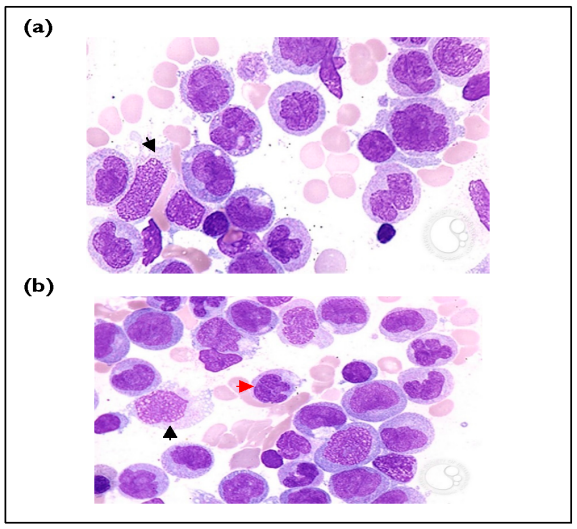


Figure 1: (**a**) Abnormal monocytes have irregular nuclear shapes (black arrow) [6]. (**b**) Abnormal promonocytes (red arrow) and monocytes (black arrow) are predominant in the bone marrow, a key feature observed in CMML [7].

2. Literature Search Strategy

The literature analysis took a narrative approach to explore research on CMML. PubMed, Google Scholar, Blood Cancer Journal, Frontiers in Oncology or Immunology, the American Journal of Cancer Research, and relevant eBooks were examined using keywords like "CMML", "Relapse", and "Allogeneic HSCT". Studies published between 2016 and 2024 were prioritized, focusing on peer-reviewed articles, clinical trials, and high-quality research. Titles, abstracts, and full texts were systematically screened to extract key insights into clinical and therapeutic advances. Moreover, a few past articles were included to give foundational knowledge. ChatGPT (OpenAI, version GPT-4) was utilized for tasks such as shortening sentences, suggesting alternative words, and enhancing text fluency. Additionally, QuillBot's AI assisted with rephrasing and grammar correction to enhance clarity. All changes made with these tools were carefully checked, corrected, and approved by the authors to ensure scientific accuracy and consistency with the manuscript's objectives.

3. Discussion

3.1. Pathophysiology and Factors Contributing to Relapse in Chronic Myelomonocytic Leukemia (CMML)

CMML is a type of blood cancer that shows features of both myeloproliferative neoplasms and myelodysplastic syndromes. The condition is characterized by persistent monocytosis greater than 1×10^9/L in the peripheral blood, absence of the Philadelphia chromosome and the BCR-ABL1 fusion oncogene, and absence of the PDGFRA or PDGFRB gene rearrangements. Additionally, it is defined by fewer than 20% blasts and promonocytes in both the peripheral blood and bone marrow as shown in Figure 1b, along with dysplasia in one or more myeloid lineages as shown in Figure 2 [8,9]. If convincing myelodysplasia is not present, the diagnosis of CMML can still be made if other criteria are met, including the presence of an acquired clonal cytogenetic or molecular genetic abnormality in bone marrow cells, or persistent monocytosis for at least three months with other causes of monocytosis excluded [9]. CMML is classified into two categories, CMML-1 and CMML-2, based on the percentage of blasts in the peripheral blood and bone marrow. The median age at diagnosis is 65–75 years, with a male predominance of 1.5–3:1. The etiology of CMML remains largely unknown, although occupational and environmental carcinogens, as well as ionizing irradiation, are possible contributing factors. The peripheral blood and bone marrow are always involved in CMML, with the spleen, liver, skin, and lymph nodes being common sites of extramedullary leukemic infiltration [4,9].

The clinical, hematological, and morphological features of CMML are heterogeneous, ranging from predominantly myelodysplastic to mainly myeloproliferative in nature. Common presenting complaints include fatigue, weight loss, fever, and night sweats. Splenomegaly and hepatomegaly are also frequently observed, particularly in patients with leukocytosis. Genetic and molecular factors play a significant role in the pathophysiology of CMML, particularly in the context of relapse. Clonal cytogenetic abnormalities are found in 20–40% of patients. Common abnormalities include trisomy 8 (+8), monosomy 7 (-7) as seen in Figure 3, deletion of the long arm of chromosome 7 (del(7q)), and structural abnormalities of 12p. Mutations

2025, Vol. 1, Article ID. 2024.0002
https://doi.org/10.69709/CIConnect.2024.193713

in the RAS gene family (e.g., NRAS and KRAS) are also significant and are observed either at diagnosis or during the disease course. The occurrence of these mutations can trigger cell proliferation and survival, which may lead to disease progression and relapse. Other genetic mutations often found in CMML include TET2, SRSF2, ASXL1, and RUNX1. Several other cellular processes, such as epigenetics regulation, the splicing machinery, and transcription factor function are also affected by these mutations, which further contribute to the complexity and progression of the disease [9].

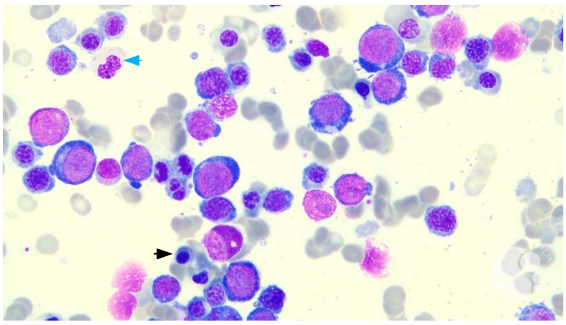


Figure 2: A bone marrow smear of a patient with MDS- multilineage dysplasia, showing left shifted granulopoiesis, one hypo granular metamyelocyte (blue arrow), and expanded erythropoiesis with dysplastic features, including binucleated forms and irregular nuclear contours (black arrow) [10].

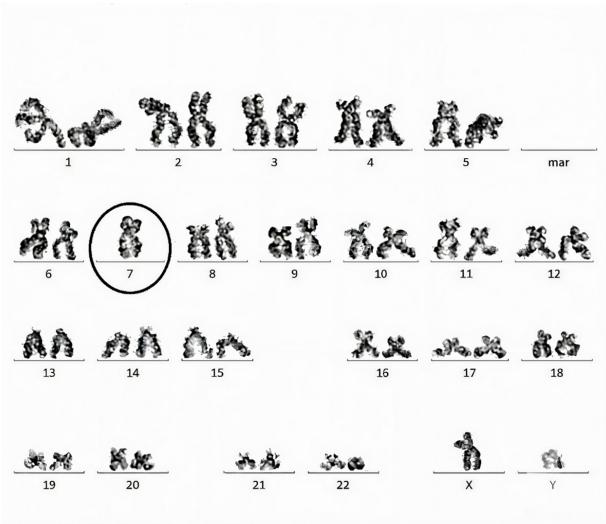


Figure 3: Using conventional cytogenetic analysis, monosomy 7 has been discovered in an 80-year-old male patient with CMML-1 [11].

The bone marrow microenvironment also plays a crucial role in CMML pathophysiology and relapse. The microenvironment provides a supportive niche for cell growth and survival of leukemic cells, promoting interactions between leukemic cells, stromal cells, extracellular matrix components, and signalling molecules. This supportive environment may protect leukemic cells from chemotherapy induced apoptosis and result in minimal residual disease, leading to relapse. In addition, changes in the bone marrow microenvironment, such as increased fibrosis and altered cytokine profiles, may further promote the survival and expansion of leukemic cells. In CMML, the bone marrow microenvironment is categorized by altered levels of cytokines and growth factors, which can promote the survival and proliferation of leukemic cells. For instance, elevated levels of GM-CSF and IL-6 are commonly seen in patients with CMML. Bone marrow fibrosis, which happens in almost 30% of CMML patients, can influence the progression of the disease as well as affect the treatment response. The presence of fibrosis is associated with a more severe disease course and poor prognosis. Immune factors also greatly influence the relapse of CMML [9].

In CMML, the immune system's ability to recognize and eliminate leukemic cells may be impaired, leading to immune evasion and disease persistence. The upregulation of immune checkpoint molecules, like PD-1 and CTLA-4, in leukemic or immune cells within the bone marrow microenvironment can contribute to immune suppression and allow for the tolerance of leukemic cells. Moreover, individuals with CMML often experience dysfunctional immune responses, including impaired T-cell activity and altered cytokine production, which can obstruct effective anti-leukemic immune responses and contribute to relapse. MDSCs are frequently elevated in CMML, playing a critical role in immune suppression and disease progression. These cells further inhibit anti-tumor immune response by suppressing T-cell function and promoting a tumor-supportive environment, ultimately complicating the disease and leading to poorer outcomes. In terms of immunophenotype, CMML cells typically show the presence of myelomonocytic markers such as CD33 and CD13, while the expression of other markers like CD14, CD68, and CD64 can vary. It is also common to see abnormal expression patterns, such as decreased expression of CD14 and HLA-DR, or increased expression of CD56 [9]. These aberrant immunophenotypes can be detected by flow cytometry, which is valuable for diagnosing CMML and monitoring disease progression. An increased percentage of CD34+ cells or an emerging blast population with an aberrant immunophenotype is associated with early transformation to AML, highlighting the importance of immunophenotypic analysis in assessing disease status and prognosis. Understanding the interplay of genetic and molecular factors, the role of the bone marrow microenvironment, and immunological aspects is crucial in addressing the challenges of relapse in CMML. Advances in molecular and genetic profiling, as well as a

deeper understanding of the bone marrow microenvironment and immune system interactions, are essential for developing targeted therapies and improving outcomes for CMML patients [9].

3.2. Comprehensive Strategies for Managing Relapsed Chronic Myelomonocytic Leukemia (CMML): Treatments and Stem Cell Therapy

CMML is a complex hematological malignancy characterized features of both myelodysplastic syndromes and myeloproliferative neoplasms, which complicates its management, especially in cases of relapse. The therapeutic approach to relapsed CMML encompasses a combination of chemotherapy, targeted therapy, immunotherapy, and stem cell therapy. Recommendations for treatment differ, depending on the specific subtype of CMML, the patient's age, and other individual medical conditions [4,12].

3.2.1. Customized Treatment

As earlier stated, it is essential to customize treatment strategies for CMML based on patient characteristics and disease risk following diagnosis. Patients with asymptomatic, low-risk CMML, such as those classified as CMML-0 by the WHO, generally experience a slow disease progression and have a low likelihood of developing AML. In these patients, close monitoring without immediate intervention is preferred to avoid treatment-related complications and maintain quality of life [4]. However, as outlined by the European Hematology Association and the European LeukemiaNet, patients with symptomatic or elevated-risk CMML distinguished by indicators such as hemoglobin levels falling below 10 g/dL, bone marrow blasts exceeding 5%, escalating leukocytosis (greater than 30×10^9/L), noticeable splenomegaly, extramedullary manifestations (like skin lesions or pleural effusions), and systemic symptoms such as fever or weight loss require immediate treatment to reduce mortality and prevent disease progression. Enhancing the treatment for high-risk CMML patients involves offering successful treatment choices that alter the advancement of the condition. The main goals of management are to maintain the patient's quality of life while achieving long-term disease control, and to avoid clonal evolution and transition to AML [4].

3.2.2. HMAs

Hypomethylating agents (HMAs), such azacitidine (AZA) and decitabine (DAC), are commonly used to treat myeloid neoplasms, including CMML [2]. These agents have demonstrated efficacy in CMML by inhibiting DNA methyltransferase, inducing hypomethylation that helps restore normal gene function and improves cell growth regulation. AZA has been prescribed since 2004 and DAC since 2006 in the US, both with approval from the Food and Drug Administration for the treatment of MDS and CMML. In Europe, AZA is approved only for the treatment of dysplastic CMML-2, while DAC remains unapproved, leading to off-label prescribing in many cases [4,13,14]. Furthermore, HMAs have verified effectiveness in managing CMML, especially in patients with proliferative features (MP CMML), by decreasing leukocytosis, improving splenomegaly, and decreasing extramedullary lesions. Research have reported that 45% of patients experienced a 50% reduction in spleen size after HMA treatment. Clinical trials have shown that HMAs can result to a moderate bone marrow (hematologic) responses and symptom improvement in CMML patients, with response rates ranging from 25% to 75% [4,14]. The overall response rate is about 50%, with complete response rates of 10–20%. The majority of patients show improvement after three rounds of treatment, with a median overall survival of about 29 months (ranging from 12 to 37 months) [13]. In patients with higher-risk CMML, defined as those with $\geq$10% blasts or classified as higher-risk by the CMML CPSS, treatment with HMA has demonstrated better outcomes compared to hydroxyurea or chemotherapy. However, responses to HMAs generally do not last long, and the prognosis after a loss of response is poor, with a median overall survival of only six months. Approximately half of the patients who experience either primary or secondary failure of HMAs go on to develop AML [13]. Identifying patients who are likely to benefit from HMA treatment continues to pose significant challenges. Recent molecular studies indicate that patients with TET2 mutations, in the absence of ASXL1 mutations, may experience improved ORR and CR rates; however, there are conflicting findings regarding these mutational patterns. Current research is aimed at leveraging these biomarkers to forecast HMA resistance and treatment response, yet no reliable biomarker has been established to predict outcomes for HMA therapy in CMML. As a result, HMAs have proven to be effective in controlling the disease course, improving symptoms, and preventing the development of AML in patients at higher risk of CMML [13].

3.2.3. Combination Therapy

The combination of Azacitidine, Lenalidomide, and DLI holds considerable promise as an initial treatment option for myeloid malignancies that experience relapse following allo-HSCT. A phase II trial conducted with 50 patients who had experienced relapses of MDS, AML, or

2025, Vol. 1, Article ID. 2024.0002
https://doi.org/10.69709/CIConnect.2024.193713

CMML showed a 56% overall response rate, with 50% of participants achieving CR. Lenalidomide, administered at doses of up to 5 mg/day, was safely incorporated into the treatment regimen without exacerbating GvHD or inducing excessive toxicity. The treatment combination resulted in long-lasting outcomes, with 80% of patients sustaining CR for approximately 15 months. Side effects, such as hematologic toxicities (neutropenia in 92% of cases, thrombocytopenia in 80%, and anemia in 36%) and GvHD, were relatively common but controllable, implying that this treatment could lead to a substantial improvement in patient outcomes for those with relapsed myeloid malignancies following allo-HSCT [15].

3.2.4. Intensive Chemotherapy

Chemotherapy continues to be a crucial part of managing CMML, particularly in the process when patients are preparing for allo-HSCT. Intensive chemotherapy treatments often include cytarabine, a DNA synthesis inhibitor, and other cytotoxic medications focused on achieving full remission by removing malignant cells prior to transplantation. Achieving remission is important because it has a big impact on overall and relapse-free survival rates. When considering a transplant, intensive chemotherapy to remove cancerous cells might be an option [4]. However, because the patient group is often older and may have other health problems, this approach might have safety risks. Past research shows that reaching CR before HSCT is a key factor in predicting good results, such as lower relapse rates and better overall survival. Therefore, treatment plans should aim to improve responses before the transplant, reduce side effects, and be adjusted to meet each patient's specific needs, including their age, the severity of their condition, and their overall health [4].

3.2.5. Targeted Therapies

Besides the treatments that are already known, new treatments that focuses on specific distinct features of blood cancers, like CMML, are being made. These new treatments aim to directly target important pathways and molecules involved in malignant cell development. Some of these treatments include drugs that block Janus kinase 2, like ruxolitinib and pacritinib. These drugs are designed to interrupt abnormal signaling pathways that are associated with the growth and survival of cancer cells. Other drugs, like tipifarnib and trametinib, block the RAS/MAPK pathway, which helps reducing cell growth by targeting key signaling proteins. Tagraxofusp (Elzonris^{TM}, SL-401) is an innovative targeted medicine that uses diphtheria toxin coupled with IL-3 to attack cancer cells [4,15]. Results from an ongoing phase 1/2 clinical trial in R/R CMML, published by Patnaik et al., demonstrated promising outcomes. Among patients with baseline splenomegaly (8/8), all showed a spleen response, with 75% (6/8) achieving a reduction in spleen size 50% or more. Additionally, 60% of patients with a baseline spleen size $\geq$5 cm achieved a similar reduction, and two patients achieved bone marrow CRs [16]. Lenzilumab inhibits GM-CSF, which promotes tumor development. Furthermore, H3B-8800 suppresses the spliceosome complex, a key regulator of gene expression in cancer cell, offering a novel approach to disrupting malignant pathways [4].

3.2.6. Allogeneic HSCT

For individuals diagnosed with CMML, allo-HSCT represents the sole treatment option with the potential for a cure, especially in younger and healthier patients. In cases where allo-HSCT is not an immediate option, the emphasis of treatment shifts to symptom management, long-term disease control, and the prevention of clonal evolution into AML [4]. To effectively address CMML relapse, it is crucial to implement comprehensive strategies, including stem cell therapy. Allo-HSCT is often preferred due to its ability to generate a strong GVL response, where donor immune cells target and eliminate recipient malignant cells. This reduces the risk of relapse and improves survival; however, severe GvHD can cause significant morbidity and mortality. Despite this, GvHD and GvL are closely related and might be caused, at least in part, by comparable immune mechanisms and cell populations [17]. Additionally, immunosuppressive medications utilized to prevent GvHD may also impair GvL, raising the likelihood of relapse. Conversely, strategies aim to enhance GvL may increase the risk of GvHD. For-instance, reducing immune suppression following HSCT resulted in remission in one-third of relapsed patients. However, 97% of those who responded developed or progressed to acute or chronic GvHD. According to Maurer and Soiffer's retrospective data, an association exist between aGvHD and improved overall survival in CMML patients undergoing HSCT, with and a stronger link between cGvHD and better overall survival observed in both univariate and multivariable analysis. Therefore, the ability to adjust the balance between GvL and GvHD has the potential to improve survival, reduce relapse rates, and enhance the quality of life for patients in CMML following HSCT [17].

3.2.7. Posttransplantation Strategies

3.2.7.1. Factors Predicting Post-Transplant Relapse

Chimerism analysis and MRD are key factors in predicting relapse following allo-HSCT. MRD represents small

groups of cancer cells that remain present following treatment and cannot be identified through traditional methods [18]. In a study involving 219 patients in remission prior to HSCT, MRD was assessed through FCM and cytogenetics, with 54% classified as MRD^+ and 23% as MRD^-. However, the effect of MRD on outcomes was significantly influenced by the conditioning regimen, with a marked difference between patients who received RI and those who received MA regimens. Specifically, an MRD^+ marker identified through cytogenetics had a more detrimental effect in RIC patients, whereas its impact was less severe in MA patients [19].

3.2.7.2. Chimerism And Residual Disease Monitoring

Various approaches can be utilized to track chimerism before and after HSCT, particularly by identifying single nucleotide polymorphisms between donors and recipients in the entire bone marrow and its sorted populations. Early declines in donor or mixed chimerism after HSCT are typically interpreted as signals of impending relapse. Chimerism monitoring in sorted CD34 cells has been used to track MRD after HSCT in patients with MDS. However, a retrospective study conducted on 36 patients with MDS/MPN found that molecular monitoring revealed a significantly higher risk of relapse in those with detectable mutations (ASXL1, CBL, TET2, or NRAS) after HSCT compared to those without detectable mutations [19].

3.2.7.3. Donor Lymphocyte Infusions (DLIs)

DLIs can be given prophylactically during periods of ongoing or declining mixed donor/recipient chimerism or in recipients who show no signs of GvHD, or as a treatment for confirmed relapse. In cases of relapsed MDS following HSCT, DLI demonstrates moderate efficacy, with prolonged post-treatment event-free survival rates ranging from 15% to 31%. A study involving 154 patients MDS or AML with MDS-related changes showed that combining DLI with azacitidine to treat relapse after HSCT resulted in a promising 2-year survival rate of 66% ± 10%, including 28 MDS patients who experienced relapse [19]. Prophylactic DLI has demonstrated positive outcomes, with long-term event-free survival rates reaching up to 77% after starting. Additionally, a phase 2 study, investigating higher azacitidine doses to prevent relapse in high-risk patients after HSCT resulted in a median event-free survival of 18-month [19]. Another study found that taking azacitidine on a monthly basis following HSCT increased cytotoxic CD8 T-cell responses to tumor antigens and enhanced relapse-free survival [19].

3.2.8. Immunotherapy and Relapse Prevention

Besides immunotherapy, checkpoint inhibitors such as PD-1/PD-L1 inhibitors have demonstrated the ability to enhance T-cell activity against cancerous cells in CMML. It has been demonstrated in early clinical trials that PD-1 blockade can induce GVL effects in AML, suggesting its potential benefit for CMML. In the context of allo-HSCT, relapse prevention could be considered crucial. This approach aims to enhance the immune response against malignant cells. Post-transplant immune modulatory strategies, like lenalidomide and CTLA-4 inhibition, have the potential to enhance the GVL effect in CMML patients, building on promising results seen in AML [20]. Furthermore, the use of prognostic models for risk assessment at diagnosis, as well as pre-transplant treatment with HMAs, will be critical to optimize the marrow response and reduce the likelihood of relapse, particularly in patients with high-risk CMML [20].

4. Future Perspectives and Limitations in Treating CMML

The future outlook for the treatment of CMML is progressively influenced by advancements in genetic research, new therapeutic options, and upcoming clinical trials; however, it's important to acknowledge that there are still considerable challenges and limitations. Recent studies in genetics have uncovered new targets that are vital for personalizing treatment strategies. Mutations in genes such as TET2 and ASXL1 have been identified as crucial factors in the development and progression of CMML. In around 60% of cases, TET2 mutations are present, whereas ASXL1 mutations are seen in approximately 40% of cases and have been identified as independent prognostic indicators in several predictive models. Mutations in SRSF2, which account for approximately 50% of cases, and alterations in the RAS pathway, found in roughly 30% of cases, play a significant role in shaping the clinical features and prognosis of the condition [21]. When compared to older models like IPSS-R and CPSS, molecularly-informed risk models such as IPSS-M and CPSS-Mol, which incorporate these genetic changes (for example, ASXL1, SRSF2, RUNX1), have been found to offer improved predictive accuracy in CMML prognosis, resulting in more precise treatment recommendations [22]. Knowing about these mutations, as well as uncommon variants including DNMT3A, NRAS, SETBP1, CBL, and RUNX1, is critical for developing targeted therapies to improve patient outcomes in CMML. These discoveries pave the way for targeted therapies that focus on particular molecular abnormalities, which could lead to more ef-

2025, Vol. 1, Article ID. 2024.0002
https://doi.org/10.69709/CIConnect.2024.193713

fective and less toxic treatments. Personalized medicine is advancing through the use of targeted inhibitors and gene-specific therapies tailored to each patient's unique genetic profile [21]. In the future landscape of CMML treatment includes the development of innovative therapies like CAR-T cell therapy, where T cells that naturally exist are genetically modified to create specific CARs that enable them to identify and destroy cancer cells. After extensive years of preclinical and clinical research, CAR-T therapy is now recognized as one of the most effective treatments, with proven success in treating B-cell lymphoma and acute lymphoblastic leukaemia [23]. However, the efficacy and safety of CLL-1 CAR-T cell therapy are now being studied in the context of CMML treatment. On the other hand, the majority of existing studies primarily focus on its use in AML, where promising outcomes have been reported. A study by Ma et al. demonstrated successful treatment of R/R AML with PD-1 silenced anti-CLL-1 CAR-T after patients failed multiline salvage therapies, including venetoclax and anti-CD38 CAR-T. One patient, a 28-year-old male relapsed after allo-HSCT and other treatments but achieved CR with a reduction in marrow blasts, and eradication of TP53 deletion after receiving CLL-1 CAR-T cell therapy. No severe toxicity was observed, and the patient was able to maintain remission for 8 months. These findings indicate the potential of CLL-1 CAR-T as a valuable choice, effective, and safe salvage therapy for AML patients with post-transplant relapse [24]. Likewise, great progress is being made in the treatment of CMML through epigenetic therapies, especially with DNMTis like decitabine (Dacogen) and 5-azacitidine (Vidaza). These modified cytidine molecules, known as nucleoside analogues, covalently interact with the catalytic sites of DNMTs to cause their irreversible inhibition and subsequent DNA demethylation. This process has the ability to reactivate tumor suppressor genes that have been silenced [25]. In addition, azacitidine [26] and decitabine [27] have been demonstrated to increase patient survival and quality of life and are authorized for clinical use in the treatment of myeloid malignancies, including CMML. To make these treatments more effective and safer, newer versions have been developed such as SGI-110, a special hypomethylating compound. Phase II clinical trials on AML and MDS have shown encouraging results, suggesting potential future application of SGI-110 in CMML [28]. In terms of therapeutic effects, CP-4200, a pro-drug of azacytidine with an elaidic acid ester, offers greater benefit compared to azacitidine [29]. Another drug, RX-3117, which is also a type of nucleoside, has shown promise in blocking DNMT1 and preventing the growth of cancer in vivo [30]. Nucleoside analogues have made great progress; however, their major drawback is a lack of specificity, which may lead to unintentional genomic instability and general hypomethylation of the genome [31]. To reduce off-target effects and improve treatment specificity, this issue highlights the importance of developing more targeted therapies. In response to these challenges, non-nucleoside DNMT inhibitors have been developed, designed to bind to the catalytic site without directly interacting with DNA. For instance, hydralazine, which has traditionally been used to manage hypertension, has shown the ability to inhibit DNMT activity and decrease the growth of malignancies by altering epigenetics [32]. Another interesting option is MG98, a second-generation antisense oligonucleotide that suppresses DNMT1 expression only, leaving DNMT3 expression unaffected. It has been tested in combination with interferon for treating metastatic renal cell carcinoma, with clinical trials have conforming its safety [33]. Furthermore, the quinoline derivative SGI-1027 has been shown to suppress DNMT1, DNMT3A, and DNMT3B without binding to DNA, highlighting its potential for more targeted treatment approaches [34]. Looking forward, advancements in genetic and molecular research are expected to identify novel therapeutic targets, enabling personalized medicine approaches for CMML that are tailored to each patient's unique profile. Innovative treatments, such as CAR-T cell therapy and advanced epigenetic therapies designed to target specific pathways, are currently in development to improve treatment precision and effectiveness [35]. However, significant obstacles remain, including overcoming resistance mechanisms associated with current medicines and ensuring selective targeting to prevent unintended genomic changes. The non-specificity of existing epigenetic agents and the balance between efficacy and safety, particularly in reducing toxicity, are critical issues that need addressing through ongoing research and clinical innovation. Future efforts must focus on developing more selective compounds that minimize off-target effects while maximizing therapeutic benefits. While current therapies have made significant progress, continued research and clinical trials are vital to refine these emerging treatments, overcome existing limitations, and integrate them into comprehensive strategies. Achieving these goals is crucial for more effective, personalized treatment approaches that improve long-term outcomes for CMML patients [36,37].

5. Conclusions

Relapse after allo-HSCT remains a critical barrier to long-term survival in patients with CMML, given the high incidence and limited effective post-relapse options. Current strategies to address this challenge include optimized co-

nditioning regimens, careful donor selection, and maintenance therapies such as: hypomethylating agents, which help maintain remission and exploit GVL effects. Immunomodulatory approaches such as DLIs and PD-1 blockade, show promise in improving GVL without exacerbating GvHD. Advances in genetic and molecular research are crucial for identifying patients who are at risk of relapse and tailoring personalized therapies. Innovative treatments like CAR T-cell therapy exist, but in the case of CLL-1 CAR-T cell therapy, there is a lack of extensive literature that specifically addresses its application in CMML. Ongoing research into its application in other hematological malignancies, such as AML, highlights opportunities for future advancements. Similarly, epigenetic therapies targeting specific molecular pathways offer hope to reduce relapse rates. The integration of these novel strategies into clinical practice, guided by ongoing and future clinical trials, could redefine relapse management in CMML. Collaborative efforts in research and personalized medicine will be critical in improving outcomes and survival rates for patients with CMML who experience relapse after transplantation.

Abbreviations

AML: Acute Myeloid Leukemia; ALLO-HSCT: Allogeneic Hematopoietic Stem Cell Transplantation; AZA: Azacitidine; ASXL1: Additional Sex Combs Like 1; BCR-ABL1: Breakpoint Cluster Region–Abelson 1; CMML: Chronic Myelomonocytic Leukemia; CTLA-4: Cytotoxic T-Lymphocyte-Associated Protein 4; CAR-T: Chimeric Antigen Receptor T-cell; Anti-CLL-1: Anti C-type lectin-like molecule-1; CBL: Casitas B-lineage Lymphoma; CR: Complete Remission; DAC: Decitabine; DNMT: DNA Methyltransferase; DLI: Donor Lymphocyte Infusion; GVHD: Graft-Versus-Host Disease; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; GVL: Graft- Versus-Leukemia; HLA-DR: Human Leukocyte Antigen - DR Isotype; HMAs: Hypomethylating Agents; IL-3: Interleukin 3; IL-6: Interleukin 6; KRAS: Kirsten rat sarcoma viral oncogene homolog; MDSCs: Myeloid-Derived Suppressor Cells; MDS: Myelodysplastic Syndrome; MPN: Myeloproliferative Neoplasm; MRD: Minimal residual disease; NRAS: Neuroblastoma RAS Viral Oncogene Homolog; ORR: Overall Response Rate; PD-1: Programmed Cell Death Protein 1; PDGFRA: Platelet-Derived Growth Factor Receptor Alpha; PDGFRB: Platelet-Derived Growth Factor Receptor Beta; RUNX1: Runt-Related Transcription Factor 1; RX-3117: fluorocyclopentenyl cytosine; SRSF2: Serine/Arginine-Rich Splicing Factor 2; SGI-110: Guadecitabine; SGI-1027: 5-Aza-2'-deoxycytidine; TET2: Ten-Eleven Translocation 2; WBC: White Blood Cells; WHO: World Health Organization

Author Contributions

A.R. provided valuable insights into manuscript preparation and organization. F.A. conducted the scientific literature search, designed the review structure, and wrote the document. A.R. contributed to manuscript writing, assisted with design, and reviewed the final version. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

Data supporting these findings are available within the article.

Consent for Publication

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

No external funding was received for this article.

Acknowledgments

We would like to extend our sincere appreciation to Dr. Mohamed Abu haleeqa, Hematologist Consultant, for providing a copy of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues ebook, which served as a vital resource in enriching the content of this article. We also acknowledge the American Society of Hematology (ASH) Image Bank for providing a comprehensive collection of hematologic images, which greatly supported this review and enriched the quality of this work. Finally, the authors acknowledge the use of ChatGPT (OpenAI, version GPT-4) for text editing when preparing the manuscript, and QuillBot's AI for paraphrasing and grammar checking.

References

[1] Baumgartner, F.; Baer, C.; Bamopoulos, S.; Ayoub, E.; Truger, M.; Meggendorfer, M.; Lenk, M.; Hoermann, G.; Hutter, S.; Müller, H.; et al. Comparing malignant monocytosis across the updated WHO and ICC classifications of 2022. *Blood* **2023**, *143*, 1139–1156. [CrossRef]

[2] Thachil, J.; Bates, I. 23–Approach to the Diagnosis and Classification of Blood Cell Disorders. In *Dacie and Lewis Practical Haematology*, 12th ed.; Bain, J.,

Bates, A., Laffan, M., Eds.; Elsevier: Amsterdam, The Netherlands, 2017.

[3] Patnaik, M.M.; Tefferi, A. Chronic myelomonocytic leukemia: 2024 update on diagnosis, risk stratification and management. *Am. J. Hematol.* **2024**, *99*, 1142–1165. [CrossRef]

[4] Kwon, J. Diagnosis and treatment of chronic myelomonocytic leukemia. *Blood Res.* **2021**, *56*, S5–S16. [CrossRef]

[5] Onida, F.; Gagelmann, N.; Chalandon, Y.; Kobbe, G.; Robin, M.; Symeonidis, A.; de Witte, T.; Itzykson, R.; Jentzsch, M.; Platzbecker, U.; et al. Management of adult patients with CMML undergoing allo-HCT: recommendations from the EBMT PH&G Committee. *Blood* **2024**, *143*, 2227–2244. [PubMed]

[6] Maslak. American Society of Hematology (ASH) | Image Bank. [Online]. 2003. Available online: https://imagebank.hematology.org/image/2151/chronic-myelomonocytic-leukemia--4?type=upload (accessed on 14 December 2024).

[7] Maslak. American Society of Hematology (ASH) | Image Bank. [Online]. 2003. Available online: https://imagebank.hematology.org/image/2149/chronic-myelomonocytic-leukemia--2?type=upload (accessed on 14 December 2024).

[8] Patnaik, M.M.; Tefferi, A. Cytogenetic and molecular abnormalities in chronic myelomonocytic leukemia. *Blood Cancer J.* **2016**, *6*, e393. [CrossRef] [PubMed]

[9] Swerdlow, S.H.; Campo, E.; Harris, N.L.; Jaffe, E.S.; Pileri, S.A.; Stein, H.; Thiele, J.; Vardiman, J.W. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th ed.; WHO press: Geneva, Switzerland, 2008.

[10] Xu, K. American Society of Hematology (ASH). [Online]. 2022. Available online: https://imagebank.hematology.org/image/63919/mds-with-multilineage-dysplasia (accessed on 15 December 2024).

[11] Yadav, A.K.; Bhargava, M. American Society of Hematology. [Online]. 2018. Available online: https://imagebank.hematology.org/collection/61453 (accessed on 16 December 2024).

[12] Anon. Healthtree.org. [Online]. Available from: https://healthtree.org/chronic-myelomonocytic-leukemia/community/what-are-treatments-for-chronic-myelomonocytic-leukemia (accessed on 19 August 2024).

[13] Liapis, K.; Kotsianidis, I. Approaching First-Line Treatment in Patients With Advanced CMML: Hypomethylating Agents or Cytotoxic Treatment? *Front. Oncol.* **2021**, *11*, 801524. [CrossRef] [PubMed]

[14] Zheng, X.; Lv, L.; Li, X.; Jiang, E. Efficacy and Safety of Hypomethylating Agents in Chronic Myelomonocytic Leukemia: A Single-Arm Meta-analysis. *Glob. Med. Genet.* **2022**, *9*, 141–151. [CrossRef] [PubMed]

[15] Schroeder, T.; Stelljes, M.; Christopeit, M.; Schmidt, E.; Scheid, C.; Mikesch, J.H.; Rautenberg, C.; Jäger, P.; Drusenheimer, N.; Holtick, U.; et al. Treatment of MDS, AML and CMML Relapse after Allogeneic Blood Stem Cell Transplantation with Azacitidine, Lenalidomide and Donor Lymphocyte Infusions - Final Results of the Prospective Azalena-Trial (NCT02472691). *Blood* **2021**, *138* (Supplement 1), 411. [CrossRef]

[16] Patnaik, M.M.; Ali, H.; Gupta, V.; Schiller, G.; Lee, S.; Yacoub, A.; Talpaz, M.; Sardone, M.; Wysowskyj, H.; Shemesh, S.; et al. Results from Ongoing Phase 1/2 Clinical Trial of Tagraxofusp (SL-401) in Patients with Relapsed/Refractory Chronic Myelomonocytic Leukemia (CMML). *Blood.* **2018**, *132*, 1821. [CrossRef]

[17] Maurer, K.; Soiffer, R.J. The delicate balance of graft versus leukemia and graft versus host disease after allogeneic hematopoietic stem cell transplantation. *Expert Rev. Hematol.* **2023**, *16*, 943–962. [CrossRef]

[18] Wang, L.; Chen, R.; Li, L.; Zhu, L.; Huang, X.; Ye, X. Prognostic implication of early minimal residual disease evaluation in patients with chronic myelomonocytic leukemia. *Am. J. Cancer Res.* **2022**, *12*, 2216–2225. [PubMed]

[19] De Witte, T.; Bowen, D.; Robin, M.; Malcovati, L.; Niederwieser, D.; Yakoub-Agha, I.; Mufti, G.J.; Fenaux, P.; Sanz, G.; Martino, R.; et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood* **2017**, *129l*, 1753–1762. [CrossRef] [PubMed]

[20] Thekkudan, S.F.; de Lima, M.; Metheny, L. Prevention of relapse after allogeneic stem cell transplantation in acute myeloid leukemia: Updates and challenges. *Adv. Cell Gene Ther.* **2020**, *3*, e77. [CrossRef]

[21] Jian, J.; Qiao, Y.; Li, Y.; Guo, Y.; Ma, H.; Liu, B. Mutations in chronic myelomonocytic leukemia and their prognostic. *Clin. Transl. Oncol.* **2021**, *23*, 1731–1742. [CrossRef]

[22] Aguirre, L.E.; Al Ali, N.; Sallman, D.A.; Kuykendall, A.T.; Chan, O.; Sweet, K.; Lancet, J.E.; Padron, E.; Komrokji, R. MDS-266 A Comprehensive Assessment of the Molecular International Prognostic Scoring System (IPSS-M) and Other Molecularly Integrated Risk Stratification Models in Chronic Myelomonocytic Leukemia (CMML). *Clin. Lymphoma Myeloma Leuk.* **2023**, *23*, S359–S360. [CrossRef]

[23] Gao, C.; Li, X.; Xu, Y.; Zhang, T.; Zhu, H.; Yao, D. Recent advances in CAR-T cell therapy for acute myeloid leukaemia. *J. Cell. Mol. Med.* **2024**, *28*, e18369. [CrossRef]

[24] Ma, Y.J.; Dai, H.P.; Cui, Q.Y.; Cui, W.; Zhu, W.J.; Qu, C.J.; Kang, L.Q.; Zhu, M.Q.; Zhu, X.M.; Liu, D.D.; et al. Successful application of PD-1 knockdown CLL-1 CAR-T therapy in two AML patients with post-transplant relapse and failure of anti-

CD38 CAR-T cell treatment. *Am. J. Cancer Res.* **2022**, *12*, 615–621.

[25] Yu, J.; Xie, T.; Wang, Z.; Wang, X.; Zeng, S.; Kang, Y.; Hou, T. DNA methyltransferases: emerging targets for the discovery of inhibitors as potent anticancer drugs. *Drug Discov Today* **2019**, *24*, 2323–2331. [CrossRef] [PubMed]

[26] Cogle, C.R.; Scott, B.L.; Boyd, T.; Garcia-Manero, G. Oral Azacitidine (CC-486) for the Treatment of Myelodysplastic Syndromes and Acute Myeloid Leukemia. *Oncologist* **2015**, *20*, 1404–1412. [CrossRef]

[27] Dhillon, S. Decitabine/Cedazuridine: First Approval. *Drugs* **2020**, *80*, 1373–1378. [CrossRef]

[28] Garcia-Manero, G.; Roboz, G.; Walsh, K.; Kantarjian, H.; Ritchie, E.; Kropf, P.; O'Connell, C.; Tibes, R.; Lunin, S.; Rosenblat, T.; et al. Guadecitabine (SGI-110) in patients with intermediate or high-risk myelodysplastic syndromes: phase 2 results from a multicentre, open-label, randomised, phase 1/2 trial. *Lancet Haematol.* **2019**, *6*, e317–e327. [CrossRef] [PubMed]

[29] Brueckner, B.; Rius, M.; Markelova, M.R.; Fichtner, I.; Hals, P.A.; Sandvold, M.L.; Lyko, F. Delivery of 5-azacytidine to human cancer cells by elaidic acid esterification increases therapeutic drug efficacy. *Mol. Cancer Ther.* **2010**, *9*, 1256–1264. [CrossRef] [PubMed]

[30] Balboni, B.; El Hassouni, B.; Honeywell, R.J.; Sarkisjan, D.; Giovannetti, E.; Poore, J.; Heaton, C.; Peterson, C.; Benaim, E.; Lee, Y.B.; et al. RX-3117 (fluorocyclopentenyl cytosine): a novel specific antimetabolite for selective cancer treatment. *Expert Opin. Investig. Drugs* **2019**, *28*, 311–322. [CrossRef] [PubMed]

[31] Flausino, C.S.; Daniel, F.I.; Modolo, F. DNA methylation in oral squamous cell carcinoma: from its role in carcinogenesis to potential inhibitor drugs. *Crit. Rev. Oncol. /Hematol.* **2021**, *164*, 103399. [CrossRef] [PubMed]

[32] Graça, I.; Sousa, E.J.; Costa-Pinheiro, P.; Vieira, F.Q.; Torres-Ferreira, J.; Martins, M.G.; Henrique, R.; Jerónimo, C. Anti-neoplastic properties of hydralazine in prostate cancer. *Oncotarget* **2014**, *5*, 5950–5964. [CrossRef]

[33] Amato, R.J.; Stephenson, J.; Hotte, S.; Nemunaitis, J.; Belanger, K.; Reid, G.; Martell, R.E. MG98, a second-generation DNMT1 inhibitor, in the treatment of advanced renal cell carcinoma. *Cancer Investig.* **2012**, *30*, 415–421. [CrossRef] [PubMed]

[34] Sun, N.; Zhang, J.; Zhang, C.; Zhao, B.; Jiao, A.O. DNMTs inhibitor SGI-1027 induces apoptosis in Huh7 human hepatocellular carcinoma cells. *Oncol. Lett.* **2018**, *16*, 5799–5806. [CrossRef]

[35] Schorr, C.; Perna, F. Targets for chimeric antigen receptor T-cell therapy of acute myeloid leukemia. *Front. Immunol.* **2022**, *13*, 1085978. [CrossRef] [PubMed]

[36] Koster, E.A.; von dem Borne, P.A.; Van Balen, P.; Marijt, E.W.; Tjon, J.M.; Snijders, T.J.; van Lammeren, D.; Veelken, H.; Falkenburg, J.F.; Halkes, C.J.; et al. Risk factors for graft-versus-host-disease after donor lymphocyte infusion following T-cell depleted allogeneic stem cell transplantation. *Front. Immunol.* **2024**, *15*, 1335341. [CrossRef]

[37] Alhuraiji, A.; Naqvi, K.; Huh, Y.O.; Ho, C.; Verstovsek, S.; Bose, P. Acute lymphoblastic leukemia secondary to myeloproliferative neoplasms or after lenalidomide exposure. *Clin. Case Rep.* **2018**, *6*, 155–161. [CrossRef] [PubMed]