American Journal of BioMedicine
AJBM 2024;12 (1): 33-42
Research Article doi:10.18081/2333-5106/2024.12/33

Outcome of COVID-19 in patients with a history of acute leukemia; A Narrative Review

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Abstract

The chemotherapy and immunosuppressive medication may be associated with the suppressed immune system of a cancer patient making them susceptible to Coronavirus disease 2019 (COVID-19) with unclear mechanisms. We reviewed current studies on the clinical courses of leukemia patients with a risk of SARS-CoV-2 infection through searches in Pubmed databases and Google search engines. The criterion used for review includes their relevance to the defined review question, which is the outcome of COVID-19 among leukemic patients and the relevant therapeutic interventions therewith. Patients with acute leukemia are among the most vulnerable groups of patients at risk of severe COVID-19 outcomes with several protocol management modifications proposed. The development of COVID-19 vaccines was an important milestone in reducing the risk of contracting and developing severe COVID-19 symptoms in leukemic patients after remission status. The European Society for Blood and Marrow Transplantation (EBMT), a collaborative network of centers and individuals working in the field of BMT and cellular therapy, has been updating its recommendations since the start of the COVID-19 pandemic.

Keywords: Leukemia; COVID-19; Chemotherapy; Immunosuppression

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Received 2 November 2023; revised 3 March 20234; accepted 30 March 2024; published 6 April 2024

Introduction

The novel betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially described in Wuhan, China, in December 2019. Since then, more than 2.5 million people worldwide have been infected with coronavirus disease 2019 (COVID-19), and more than 170,000 have died. It is well known that co-existing comorbidities increase the mortality in COVID-19 infection [2]. The presence of low lymphocyte counts, frequently observed in leukemia, and other comorbidities such as advanced age are positively associated with mortality [1]. During the pandemic, many patients with hematological malignancies confronted the virus, either at the time of diagnosis or during the treatment course. It is hypothesized that patients with hematologic malignancies and concomitant COVID-19 infection may have poorer disease outcomes and worse survival rates compared to patients without the disease [3]. The acute leukemia working party of EBMT (European Society for Blood and Marrow

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Transplantation) recommended waiting for cytogenetics and molecular biology results to properly stratify the risk of the acute leukemia cases [4]. They also advised screening of COVID-19 infection before initiation of chemotherapy and consideration of omission of one cycle of consolidation in case of MRD molecular remission achievement. Patients with leukemia may be at a uniquely higher risk of developing COVID-19 for multiple reasons associated with both their underlying diagnosis and treatment as well as patient-specific factors [5]. Each leukemia subtype may also be associated with particular COVID-19-associated risks due to disease biology or associated therapy, patients with lymphoid malignancies are at higher risk of infection due to impaired humoral response caused by disease- or treatment-related hypogammaglobulinemia [6]. Immunocompromised leukemia patients with COVID-19 can also be at higher risk of superimposed bacterial or fungal pneumonia. Given the above, guidelines concerning the management of leukemia in COVID-19 high-risk periods would be helpful .

Immunomodulation

Glucocorticoid Glucocorticoids are known for their robust anti-inflammatory properties, which can help reduce the incidence of respiratory failure and mortality in patients with severe COVID-19. A large randomized controlled trial conducted by researcher investigated the use of dexamethasone in hospitalized COVID-19 patients and a total of 2104 patients were enrolled and received dexamethasone (6mg, orally or intravenously, once daily, 10 days) [7]. The study has found that compared with usual care, dexamethasone use brought significant improvements in terms of 28-day mortality in patients requiring invasive mechanical ventilatory support (29.3% vs 41.4%, RR=0.64, 95% CI: 0.51-0.81) and non-invasive mechanical ventilatory support (23.3% vs 26.2%, RR=0.82, 95% CI: 0.72-0.94). But there was no significant relationship between dexamethasone use and mortality in patients without respiratory support. Other study carried out a multicenter retrospective study on 367 HM patients with COVID-19, which showed that low-dose glucocorticoids (intravenous methylprednisolone ≤ 0.5mg/kg/d or equivalent dose of other glucocorticoids) could reduce mortality in HM patients (OR=0.31, 95% CI: 0.11~0.87, P=0.020), while doses over 0.5mg/kg/d did not benefit the patients (OR=0.75, 95% CI: 0.34 ~ 1.6, P=0.4). Considering the immunocompromised status of HM patients, careful consideration is necessary when determining the timing and dosage of glucocorticoids [8]. It is recommended that when patients present signs of infection aggravation such as decreased oxygen saturation, increased respiratory rate and elevated infection markers, low-dose dexamethasone [9] should be added to the existing treatment regimen for no longer than 10 days [11].

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Cytokine receptor antagonist SARS-CoV-2 infection

Cytokine receptor antagonist SARS-CoV-2 infection can trigger a cytokine storm characterized by the production of interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α and other cytokines [11]. A meta-analysis by research indicated that IL-6 receptor antagonists (Tocilizumab, Sarilumab) and IL-1 receptor antagonists (anakinra) could significantly reduce mortality in COVID-19 patients (OR=0.71, 95% CI: 0.57-0.89, P=0.004), but the use of tocilizumab poses a potential risk of secondary fungal infection [7]. A randomized controlled study other [11]. (2021) and the RECOVERY trial (RECOVERY Collaborative Group, 2021) both showed that anakinra and tocilizumab can significantly ameliorate disease progression and reduce mortality among severe COVID-19 patients. Notably, the majority of patients in these two studies received glucocorticoid treatment (85.9% and 82%, respectively), indicating that the clinical benefits of cytokine receptor antagonists were generated based on glucocorticoid [12]. Therefore, it is recommended to consider cytokine receptor antagonists in patients with persistent hypoxia or inflammatory responses despite glucocorticoid treatment. However, research on cytokine receptor antagonists in HM patients remains relatively limited, with a primary focus on tocilizumab. The lack of standardized reference guidelines for the indications, timing, dosage, and combination therapy of tocilizumab across diverse studies has contributed to varying conclusions. In several case reports, the addition of IL-6 pathway inhibitor (tocilizumab) to glucocorticoids improved hypoxia and prognosis in HM patients (including those with CML or MM) with severe COVID-19, and short-term use would not increase the risk of secondary infection [13]. However in a retrospective study (García-Suárez et al., 2020) involving 692 patients with HM and COVID-19, 318 (46%) patients received systemic corticosteroids and 132 (19%) patients received tocilizumab. This study demonstrated an association between tocilizumab administration and an increased mortality rate in HM patients with mild to moderate COVID-19 (HR=5.94, 95% CI: 1.80~19.6, P=0.002), while no significant difference was observed in severe/critical patients (HR=0.87, 95% CI: 0.62~1.23, P=0.40) [14]. These findings suggest that tocilizumab may have potential utility in mitigating hyperactive cytokine responses specifically in severe/critical COVID-19 cases. Nevertheless, given the complex cytokine and inflammatory pathways and the intricate immunological conditions in HM patients, randomized controlled trials are warranted to elucidate the specific roles of tocilizumab and other cytokine receptor antagonists in patients with HM and COVID-19.

Treating patients with acute leukemia during a COVID-19 pandemic

Treatment of acute leukemia through COVID-19 can be particularly challenging. One must weigh the treatment of a lethal, acute illness requiring aggressive therapy against the systemic limitations of inpatient stays, frequent clinic visits, and increasingly restricted blood product supply. The development of several targeted therapies to treat both ALL and AML may allow a reduction of dose intensity while preserving efficacy and the potential of cure. Furthermore, The treatment of ALL was historically based on pediatric-inspired intensive regimens that use

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multiagent chemotherapy, including steroids [15]. The recent development of less myelosuppressive regimens incorporating the CD3-CD19 bispecific antibody, blinatumomab, and the anti-CD22 conjugated antibody, inotuzumab ozogamicin, have improved treatment options and demonstrated overall safety and efficacy, particularly in older patients [16]. All newly diagnosed patients with ALL and those receiving consolidation therapy should be screened for COVID-19, including a baseline computed tomography (CT) of the chest without contrast due to the potential for false-negative PCR from the nasopharyngeal swab, regardless of symptoms. The management of patients with leukemia during the COVID-19 pandemic may be challenging. During high-risk COVID-19 periods, with optimal preventive measures and testing for COVID-19 (nasal swab, serology, chest CT), the risk of infection is still low although the mortality may be higher in patients with leukemia and COVID-19 [17]. Therefore, the risk of COVID-19 complications should be weighed very carefully against restricting access of patients with leukemia to highly specialized centers and advocating for regimens without known equivalent curative potential. Efforts to reduce patient and staff exposure while maintaining optimal care should be prioritized. Utilizing less intensive therapies, reducing patient visits, and establishing collaborative care at local centers or through telemedicine are some ways to safely provide effective treatment. There is a large knowledge gap on how to treat COVID-19-positive patients due to a lack of experience. However, treatment decisions need to be individualized based on patient-related factors, the risk of added toxicity from chemotherapy, and the feasibility of treatment administration.

Poor Outcome of patients with acute leukemia are predisposed to COVID-19

Dysregulation of several components of innate and acquired immunity is noted in most malignancies [17]. Patients with AML have higher expression of negative regulatory receptors and proliferation of regulatory T cells. This is potentiated by disruption of normal NK cell development and defective metabolism, further attenuating the host response. Patients with AML have an added risk owing to myelosuppression and myeloid dysfunction, and patients with ALL have an added risk owing to hypogammaglobulinemia and prolonged use of steroids. All these factors work in tandem to increase the risk of various viral and fungal infections, including uncommon pathogens in patients with acute leukemia [18]. The highest risk of COVID-19 infection has been noted with ALL, followed by essential thrombocytosis and AML. This surprising finding indicates the undefined role of many factors beyond myelosuppression in mediating the risk of infection and disease. From the beginning of 2020, several reports indicated a higher risk of mortality with COVID-19 in patients with cancer [19]. However, as treatment of acute leukemia can often not be delayed, COVID-19 infections were documented in several patients with hematologic cancers, providing valuable insights into infection risk and outcomes.

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Stem Cell Transplantation

Indications for stem cell transplantation in acute leukemia include high-risk disease (based on cytogenetic and mutation data or inadequate response to therapy) or refractory disease. Patients with AML who need a transplant should be referred as soon as possible, as a delay leading to even minimal residual disease positivity is associated with disease progression and inferior survival [20]. It must be emphasized that the risk of donor-to-patient transmission of COVID-19 is low, and blood-borne transmission has not yet been documented despite the presence of low-level viremia. However, if a donor tests positive for COVID-19, temporary deferral is universally advised. The European Bone Marrow Transplantation (EBMT) guidelines recommend a 3-month deferral if a donor tests positive for COVID-19, and a 28-day deferral in case of potential exposure to an infected individual [21]. It is vital to adapt these guidelines to local practice, as a delay of 1 to 3 months may not be feasible for certain high-risk patients. This principle is mirrored in the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines, which recommend consideration of a donor with a recent infection after 28 days on a case-by-case basis.

According to the current recommendations of the ASH, the European Society for Blood and Marrow Transplantation (ESBMT), intensive chemotherapy should be offered to AML patients who are considered eligible for intensive chemotherapy [22]. However, to avoid hospitalization and to reduce transfusion frequency in the case of local outbreaks or a shortage of beds and blood supplies, low-dose therapy with azacytidine in combination with venetoclax may be considered as an alternative, especially in those patients with reduced performance status [23]. Large data sets are missing for adult ALL patients with COVID-19 due to the low ALL incidence in adults. The ASH recommends delaying systemic ALL treatment. Since the detection of SARS-CoV-2 can be prolonged for up to 91 days in ALL patients, it remains unclear how to proceed with these patients [24]. However, intrathecal therapy should not be delayed in the case of central nervous system symptoms [6]. Since corticosteroids are essential components of ALL treatment, it is highly recommended by the ESBMT to proceed with a standard dosage of corticosteroids in ALL patients, even if there might be a potential risk for provoking viral rebound [4].

Furthermore, the administration of peg-asparaginase as an essential compound in ALL treatments is challenging due to the increased risk of thrombotic events caused by COVID-19. Nevertheless, peg-asparaginase should be administered under the intensive monitoring of coagulation parameters in SARS-CoV-2-infected ALL patients according to the ESBMT recommendations [55]. For Philadelphia chromosome-positive ALL patients, it is recommended to switch the therapeutic approach to tyrosine-kinase-inhibitor-based treatment in combination with steroids rather than multi-agent chemotherapy [20]. This approach has been reported as feasible by the CAMPUS ALL Network [25]. The use of rituximab during consolidation therapy is controversial and no clear recommendations are available [26]. It is recommended to withhold

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the treatment of patients during maintenance therapy until symptoms are resolved for at least two weeks.

CAR-T therapy

Patients with acute leukemia usually require high-dose chemotherapy and long-term immunosuppressive therapy before and after HSCT or CAR-T therapy, which amplifies the risk of SARS-CoV-2 infection and death. Before the prevalence of Omicron variant, the mortality of COVID-19 patients who underwent allo-HSCT was slightly higher than that of patients who received autologous HSCT (auto-HSCT) (18.5%-35.5% vs 14.3%-33.3%) [27]. Additionally, post-transplant immunosuppressive therapy further increased the death risk. Nevertheless, have discovered that the mortality of patients receiving auto-HSCT or allo-HSCT was slightly lower than that of non-HSCT patients ($P<0.03$), which could be explained by factors such as younger age, longer post-transplant periods, fewer comorbidities, and better control of blood diseases in the transplantation group [27]. In contrast, CAR-T therapy has conferred a statistically significant excess risk of death in COVID-19 patients compared to HSCT, which can be ascribed to long-term B-cell exhaustion, hypogammaglobulinemia, loss of T-cell repertoire diversity, and exacerbation of cytokine storm caused by COVID-1. During the Omicron wave, the mortality of HSCT and CAR-T patients with COVID-19 significantly decreased compared to the pre-Omicron period. With the implantation of appropriate prophylactic and therapeutic measures, such as Evusheld injection and re-vaccination after transplantation, the mortality of HSCT patients with COVID-19 has been reduced to 0%, although that of CAR-T patients remains high, ranging from 20-25%. In summary, the mortality of HM patients undergoing CAR-T or HSCT and infected with Omicron was significantly lower than before, but CAR-T patients still experienced a higher mortality rate than others. Therefore, it is crucial to strengthen preventive and treatment measures for these vulnerable patients. Revaccination should be carried out 3-6 months after cell infusion irrespective of their vaccination status before treatment. Passive immunotherapy such as NmAbs and CCP should be actively utilized according to the patient's specific condition [28]. HM patients who have already contracted SARS-CoV-2 should carefully consider CAR-T therapy or select the appropriate timing for HSCT, and it is recommended to delay HSCT for at least 14 days until symptoms of infection have significantly improved.

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Conclusion

clinical and biochemical data of COVID-19 might be partly masked by coexisting acute leukemia; better diagnostic strategies (ie, superior CT differential techniques such as radiomics) could be used for diagnosis; individuals with compromised immune status might be subjected to a longer incubation period (although the underlying mechanisms are not known); and it remains uncertain whether the combination of chemotherapy, corticosteroids, α-interferon, and immunoglobulins could work synergistically in patients with acute leukemia and COVID-19.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

Research Article doi:10.18081/2333-5106/2024.12/33

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American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net