To the Editor
We attentively read the paper by Melike et al. [1] recently published in the Turkish Journal of Hematology. They investigated the clinical features and prognosis on invasive fungal infections (IFIs) in children with leukemia, and found that IFIs significantly increased mortality, and are poor prognostic factors in children with hematologic malignancies [1]. Therefore, physicians must be aware of rare
but potentially lethal infections. Furthermore, they also revealed that prolonged severe neutropenia was one of the major risk factors for the incidence of IFIs, and this conclusion was investigated based on 307 children with acute lymphoblastic leukemia (ALL, n=238), acute myeloid leukemia (AML, n=51) and relapsed leukemia (n=18). However, in this letter, we also highlight that another important factor may overlook on the prognosis of the IFIs in children with leukemia, which is hypogammaglobulinemia. Importantly, ALL patients have deficits in lymphocytes, resulting in hypogammaglobulinemia and impaired cell-mediated immunity predisposing to bacteria, virus and fungi infection[2]. Chemotherapy often aggravates these deficits, resulting in prolonged periods of severe neutropenia then further increasing the risk of infection[2]. Recently, Katarzyna et al[3] found that the majority of ALL patients required immunoglobulin replacement during chemotherapy. Moreover, Lange CS et al[4] also found that hypogammaglobulinemia is a poorly described complication of chemotherapy in young adults and adolescents with ALL. The majority of treated ALL patients had hypogammaglobulinemia, and infectious events during maintenance and febrile neutropenia episodes during the treatment course occurred more frequently in hypogammaglobulinemia patients compared with patients with normal IgG levels[4]. However, hypogammaglobulinemia (eg, IgG <5 g/L) or dynamic polyclonal Ig levels before or during the IFIs period were not documented or investigated in this study[1], which may overlook the role of hypogammaglobulinemia on the risk of IFIs in these childhood leukemia patients. And hypogammaglobulinemia is the hallmark of secondary immunodeficiency and increased infection risk[2]. Therefore, monitoring the polyclonal Ig levels before or during the IFIs period and calculating the cutoff Ig values for IFIs risk, could further enhance the surveillance of IFIs risk in these childhood leukemia patients. Furthermore, using Ig replacement therapy for these potential hypogammaglobulinemia patients who had these IFIs risk factors, could be a feasible method for the prevention of IFIs, further significantly reducing the mortality of these children leukemia patients[2]. And this supportive care is critical for the quality of life and longer survival of acute leukemia children patients[5, 6]. However, these hypotheses and proposes are deserved to be openly discussed and more large studies are warranted to validate the effect of hypogammaglobulinemia or other polyclonal Ig levels on IFIs in childhood leukemia patients.
References


We thank you, Dr. … for being interested in our article. Intravenous immune globulin therapy and screening for hypogammaglobulinemia are routinely performed in patients undergoing HSCT and receiving targeted therapy (CAR-T-Cell, Rituximab, Blinotumomab ..). However, the effect of routine Ig screening and its use on mortality and morbidity in ALL and AML treatment is not shown evidence-based and has been found costly. It is not routinely recommended for both the ECIL and EORTC/MSG guidelines. Patients with frequent infections can be screened and supported if IgG level is found low. In our series, we also supported our patients with frequent infections with low IgG levels ( <500 mg/dl ).

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