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by Gerhard Zugmaier, Nicola Goekbuget, Selina Luger, Mark Litzow, Gunnar Cario and Franco Locatelli

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Depletion of CD19-positive B-cells and dexamethasone premedication may result in immune suppression in patients with B-precursor acute lymphoblastic leukemia after consolidation treatment with blinatumomab

Gerhard Zugmaier[1], Nicola Goekbuget[2], Selina Luger[3], Mark Litzow[4], Gunnar Cario[5], Franco Locatelli[6]*

[1] Department of Hematology, Oncology and Immunology, Philipps University of Marburg, Germany

[2] Goethe University, University Medicine, Dept. of Medicine II, Hematology/Oncology, Frankfurt, Germany

[3] Hematology-Oncology and Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA

[4] Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN USA

[5] Department of Pediatric Oncology and Rheumatology, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany

[6] Department of Pediatric Hematology, Oncology and Cell and Gene Therapy, IRCCS Bambino Gesù Children's Hospital, Catholic University of the Sacred Heart, Rome, Italy

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*Corresponding author

Franco Locatelli, M.D., Ph.D.

Department of Pediatric Hematology and Oncology
IRCCS Ospedale Pediatrico Bambino Gesù
Piazza Sant'Onofrio, 4
00165 Rome
Italy
Phone: +39 06 68592678/2129
Fax: +39 06 68592292
e-mail: franco.locatelli@opbg.net

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G.Z. reports the following patent rights belonging to International (WO) publications: Dosage Regimen for Administering a CD19XCD3 Bispecific Antibody (WO2011/051307), Stratification of ALL patients (WO2015181683), Treatment of Pediatric Acute Lymphoblastic Leukemia (WO2010/052013), Anti-leukocyte Adhesion for the Mitigation of Potential Adverse Events (WO2014/122251), Means and Methods of Treating DLBLC (WO2012055961), Adaptive Subcutaneous Dosing of Blinatumomab in B Precursor Lymphoblastic Leukemia (WO2023062188), Prevention Of Adverse Effects Caused By CD3 Specific Binding Domains (WO2012/062596), Novel treatment of acute lymphoblastic leukemia (WO2010/052014), Dosage Regimen for Administering a CD19XCD3 Bispecific Antibody to Patients at Risk (WO2012146394), and Novel Dosing Regimen of Blinatumomab for Treatment of Aggressive Non-Hodgkin-Lymphoma with Onset of Response within 2 weeks and Novel Medication for Prevention of Neurological Adverse Events (WO2020/221792) as well as WO2025/181224. related to CD19-selective T cell engaging molecule for treating autoimmune diseases/ 5 autoimmune conditions. G.Z. also reports on holding stocks in Amgen Inc.

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Abstract

Treatment of patients with B-cell acute lymphoblastic leukemia (B-ALL) has benefited greatly from the introduction of different immunotherapy approaches targeting CD19 or CD22. In particular, when added to or when replacing some parts of chemotherapy treatment, blinatumomab, a bispecific T-cell engager which creates an immunological synapse between patient's CD3-expressing T lymphocytes and CD19-positive cells, including leukemia blasts, has shown unprecedented efficacy in preventing leukemia relapse/progression in both adults and children with either newly diagnosed or relapsed B-ALL. Despite the great anti-leukemia efficacy shown by blinatumomab, data obtained in large randomized studies in adults and children with newly diagnosed B-ALL have shown that the benefit of immunotherapy has, in part, been offset by an increased risk of infections, which can even occur long after completion of immunotherapy. Blinatumomab is also able to lyse normal B lymphocytes, and the resulting long-lasting, profound B-cell aplasia may lead to severe hypogammaglobulinemia, in turn increasing the incidence of infectious complications. Premedication with dexamethasone is widely used for mitigation of neurotoxicity and other systemic toxicities related to initial exposure to blinatumomab, but the dose usually employed does not derive from well-conducted studies aimed at identifying the recommended steroid dose. In addition, there is no robust evidence of a neuroprotective effect of Dexamethasone. This Spotlight Review aims to highlight the importance of monitoring immunoglobulin levels and to provide guidelines for initiation and continuation of immunoglobulin replacement therapy. In addition, we focus on need to conduct studies properly addressing the identification of optimal corticosteroid doses, regimens, and timing.

Impact of Immune Suppression with Blinatumomab

In the last decade, the use of immunotherapy has revolutionized the therapeutic landscape of patients with B-cell precursor acute lymphoblastic leukemia (B-ALL), allowing for better disease control. In particular, two large randomized controlled Phase 3 clinical trials have demonstrated a significant improvement in overall survival (OS) and event– free survival (EFS) through the addition of blinatumomab, a bi-specific T-cell engager targeting CD19, to the chemotherapy regimen in both children and adults, treated with varying chemotherapy regimens. However, not surprisingly, when blinatumomab has been given in addition to chemotherapy, there has not been a marked improvement in reduction of treatment complications in the experimental immunotherapy arm versus control arm. In particular, infection rates have been shown to be higher in the blinatumomab arm compared with the chemotherapy control arm as documented below. This increase in infection rates has been noted in all age groups [1-3]. Thus, the benefit of immunotherapy has, in part, been offset by increased infections, which can even occur long after completion of immune therapy [1-3].

In the E1910 trial, adults aged 30-70 years with newly diagnosed Philadelphia chromosome-negative B-ALL in measurable residual disease (MRD)-negative complete remission (CR) were randomized to receive either consolidation chemotherapy alone or alternating cycles of blinatumomab and chemotherapy [2]. Grade 3 or higher infections were reported in 31% of patients in the blinatumomab-containing arm and 21% of patients in the chemotherapy-only arm [1;2].

In the AALL1731 trial conducted by the Children's Oncology Group (COG), children with newly diagnosed standard-risk B ALL-were randomized to be treated with either chemotherapy alone or the same chemotherapy treatment plus two non-sequential cycles of blinatumomab [3]. The trial included 2 cohorts of patients, a standard-risk average-relapse-risk (SR-Avg) cohort and a standard-risk high-relapse-risk (SR-High) cohort. In the SR-Avg relapse-risk cohort, selected grade 3 or higher sepsis or catheter-related infections occurred in 14.8% of patients assigned to blinatumomab plus chemotherapy and in 5.1% of patients assigned to chemotherapy alone [3]. In the SR-High relapse-risk cohort, the corresponding incidences were 20.9% and 17.0%, respectively. Importantly, severe infections occurred also late after Blinatumomab administration, e.g. during maintenance treatment (3).

Blinatumomab has been also successfully employed to replace some elements of chemotherapy in both newly diagnosed and relapsed B-ALL patients. In the recently published AIEOP-BFM ALL 2017 trial [4], newly diagnosed Philadelphia chromosome–negative B-ALL high-risk (HR) pediatric patients (up to the age of 18), after the receipt of induction and consolidation treatment and of one cycle of intensive chemotherapy, were randomly assigned to receive two 28-day cycles of blinatumomab (experimental group) or two courses of intensive chemotherapy (control group). The infection rate during the randomized phase of therapy was lower (23.9%) for children who received blinatumomab as compared to that of patients treated in the control group (69.4%). However, while in patients who subsequently underwent allogeneic stem cell transplantation the post-transplant death rate was much lower in the group of patients who have received blinatumomab instead of chemotherapy (2.5% vs. 16.4%), the replacement of

chemotherapy by blinatumomab did not prevent fatal infections in subsequent phases of treatment (delayed intensification and maintenance) or even after discontinuation, since 8 patients in the blinatumomab group and 6 in the control group died while in CR1 [4].

In the setting of relapsed/refractory B-ALL, 2 studies have tested the safety and efficacy of replacing chemotherapy elements with blinatumomab [5,6]. In the 215 Amgen-sponsored trial on children with HR first-relapse B-ALL, one block of consolidation chemotherapy before allogeneic hematopoietic cell transplantation was replaced by one cycle of blinatumomab. Whereas the rate of grade 3 or higher febrile neutropenia was 3.7% in the experimental arm and 25.5% in the control arm, the overall rate of grade 3 or higher infections was 18.5% in the experimental arm and 9.8% in the control arm [5]. The COG AALL1331 trial enrolled children with first relapse of B-ALL. In the HR subset of patients, two blocks of chemotherapy were replaced by two cycles of blinatumomab in the experimental arm [6]. In the standard-risk relapse cohort, three cycles of blinatumomab were added to the experimental arm, alternating with chemotherapy. The trials reported safety data only for the period of blinatumomab treatment [6,7]. In the experimental arm of the HR patients containing blinatumomab incidences of infection (15%), febrile neutropenia (5%), sepsis (2%), and mucositis (1%) were lower than those recorded in the control arm [infection (65%), febrile neutropenia (58%), sepsis (27%), and mucositis (28%)] [6]. In the standard risk cohort, the rate of infections Grade 3 was 27% in the control arm and 2% in the experimental arm, the rate of febrile neutropenia Grade 3 was 48% in the control arm and 10% in the experimental arm [7].

Overall, most of the data summarized above indicate a safety benefit of blinatumomab during blinatumomab treatment and in the transplant setting, but after completion of blinatumomab treatment in non-transplanted patients the rate of infections is not improved or maybe even worse than that recorded in patients given only chemotherapy.

Immunosuppression is multifactorial and may be caused by B-cell depletion, dexamethasone prophylaxis used for preventing blinatumomab-related toxicities, and/or decreased neutrophils. Because CD19 is expressed by both malignant and normal B cells, blinatumomab treatment causes rapid depletion of B cells and may also deplete CD19-positive plasmablasts (Figure 1). [8]. B- cell aplasia (BCA) is a recognized on- target/off-tumor permissive toxicity that develops following treatment with B- cell targeting immunotherapies. The detrimental impact on immunoglobulin production and, thus, on their serum levels occurs early during blinatumomab administration and extends beyond completion of blinatumomab treatment [9]. After treatment with blinatumomab, recovery of immunoglobulin M has been reported to precede that of immunoglobulin G and immunoglobulin A [9]. Recovery of IgM occurred after approximately 1 year after blinatumomab treatment, recovery of IgG occurs after approximately 1.5 to 2 years, significant recovery of IgA was not observed after a follow up of 500 days [9]. The sample size on which these data were produced was low and larger studies are warranted to definitively confirm these findings. This different recovery in immunoglobulin serum levels is explained by the observation that, whereas *naive* B cells reappeared earlier, as shown by IgM serum levels, memory B cells and plasma cells reappear later as shown by IgG and IgA levels [9] The age of the patient must also be considered when assessing the impact of blinatumomab on B-cell function. Indeed, in a recently published study on 30 infants with KMT2A-rearranged B-ALL, blinatumomab administered after induction

therapy led to an IgG reduction, with near-complete recovery occurring before the end of chemotherapy treatment, supporting the concept that the impact of blinatumomab on recovery of normal B cells may differ according to the age of the patient [10]. Hematopoietic cell transplantation after blinatumomab treatment may also affect B-cell recovery and, thus, immunoglobulin production. Indeed, the adoptive transfer of donor-derived, mature B cells, as well as the B-cell neogenesis from donor hematopoietic stem cells, may facilitate the recovery of the B-cell compartment. Future trials that utilize blinatumomab should integrate the prospective longitudinal assessment of immune function and reconstitution to enable the development of effective strategies aimed at minimizing the risk of infections.

Impact of Immune Suppression with Dexamethasone

Corticosteroid premedication, especially dexamethasone, has been included in all treatment protocols to prevent blinatumomab-associated neurotoxicity and first dose-related side effects. [11]. However, the benefit of dexamethasone and the optimization of dose in this setting has never been investigated prospectively. In addition, it has to be considered that dexamethasone can partly contribute to increase the risk of infections (Figure 1).

Recent real-world data have not demonstrated a clear benefit in terms of neurotoxicity prevention by dexamethasone [12], raising the question whether administration of this corticosteroid before starting blinatumomab infusion to prevent neurotoxicity is truly necessary.

Additionally, the current US prescribing information contains different corticosteroid premedication regimens according to age and treatment setting, without clear data advocating for these divergent indications. In particular, in relapsed or refractory B-ALL of adult patients, premedication with 20 mg of dexamethasone intravenously or orally 1 hour prior to the first dose of blinatumomab of each cycle, prior to a step dose (such as Cycle 1 Day 8), and when restarting an infusion after an interruption of 4 or more hours is recommended. For pediatric patients, premedication with 5 mg/m^2 of dexamethasone intravenously or orally, to a maximum dose of 20 mg, prior to the first dose of blinatumomab in the first cycle, prior to a step dose (such as Cycle 1 Day 8), and when restarting an infusion after an interruption of 4 or more hours in the first cycle, is recommended, as well [13].

Adult patients with MRD-positive B-ALL are recommended to be premedicated with prednisone 100 mg intravenously or with an equivalent dose of other corticosteroids (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of blinatumomab in each cycle. Pediatric patients treated with blinatumomab for MRD-positive B-ALL are recommended to receive premedication with 5 mg/m^2 of dexamethasone intravenously or orally, to a maximum dose of 20 mg, prior to the first dose in the first cycle and when restarting an infusion after an interruption of 4 or more hours in the first cycle [13].

In adults receiving blinatumomab in the consolidation phase, even if MRD negative, pre-medication with dexamethasone 20 mg intravenously is to be administered within 1 hour prior to the first dose of blinatumomab of each cycle. For MRD negative pediatric patients, it is advised to pre-medicate with 5 mg/m^2 of dexamethasone intravenously or orally, to a

maximum dose of 20 mg prior to the first dose of blinatumomab in the first cycle and when restarting an infusion after an interruption of 4 or more hours in the first cycle [13].

In children, dexamethasone has been left off as premedication starting from cycle 2 with no evidence of a negative impact [13].

This section of the United States prescribing information was based on the data of the single-arm multicenter phase II study preceded by dose evaluation to investigate the efficacy, safety, and tolerability of blinatumomab in pediatric and adolescent patients with relapsed/refractory B- ALL. Dexamethasone administration was only mandatory before cycle 1.

The current EU prescribing information is similar with the exception that premedication is suggested at the start of consolidation cycles for all age groups. [14].

Overall, dexamethasone administration as premedication in the consolidation setting beyond cycle 1 is not necessary, since it does not prevent neurotoxicity. In addition, severe cytokine release syndrome in the consolidation setting of patients given blinatumomab while in CR is extremely rare, because the severity of this complication is associated with the burden of CD19+ elements in blood or bone marrow. Before cycle 1, dexamethasone is recommended since the 1st dose effects also include allergic reactions caused by the murine nature of the blinatumomab molecule. However, there is no rationale supporting the dose currently applied and for using dexamethasone instead of other types of corticosteroids.

Conclusions

This manuscript addresses two related supportive-care questions: first, how the humoral compartment of the immune system should be strictly monitored during and after blinatumomab therapy; and second, how the recommended dexamethasone premedication dosing can be made evidence-based.

The National Comprehensive Cancer Network pediatric ALL guideline recommends monitoring patients for the occurrence of hypogammaglobulinemia both during and after therapy until B-cell recovery. It recommends immunoglobulin replacement therapy in the presence of immunoglobulin G serum levels below 400 mg/dL or below the age-adjusted lower normal limit, particularly in patients at high risk of infections or with recurrent or active infections [15]. A recently published article makes similar recommendations for children [16]. In the EU, similar recommendations have been developed. However, the application is per label restricted to patients with recurrent infections, a recommendation which can become an issue in terms of reimbursement.

Proposed consensus statements

A significant proportion of patients given CD19- or CD22-directed immunotherapy are not being screened or properly identified as having hypogammaglobulinemia both before and after blinatumomab administration. Monitoring of immunoglobulin levels both before and after blinatumomab may allow for earlier identification of risk for developing severe, life-threatening infection and identify patients who may benefit from immunoglobulin

replacement, which may, in turn, help avoid excess morbidity and mortality. Thus, practically, serum immunoglobulin levels, including at least immunoglobulin G, should be measured before initiation of blinatumomab. Thereafter, serum immunoglobulin levels should be reassessed periodically during and after blinatumomab treatment (Figure 1). The monitoring interval should be individualized in each patient by baseline immunoglobulin concentrations, age, infection history, accompanying chemotherapy, previous transplantation, and the planned number of treatment cycles.

Follow-up of immunoglobulin G and clinically important infections should continue after completion of blinatumomab in patients with persistent hypogammaglobulinemia, or presenting recurrent or severe infections, prolonged B-cell depletion, or other risk factors for delayed immune recovery.

B-cell recovery, defined as $\geq$ 10 CD19- positive B cells/μL confirmed on a subsequent test $\geq$ 2 weeks apart [17] should not be used as the sole criterion for discontinuing immune monitoring, because *naïve* B-cell recovery may precede restoration of memory B-cell and plasma-cell function.

A recent review summarizes the current thinking about hypogammaglobulinemia in children [16]. Recommendations for immunoglobulin monitoring and replacement should include both children and adults. Immunoglobulin replacement should be considered for clinically significant immunoglobulin deficiency, particularly persistent marked hypogammaglobulinemia accompanied by recurrent, severe, persistent, or otherwise clinically important infections. For example, in a patient with immunoglobulin G serum levels less than 400 mg/dL, replacement therapy is recommended even if this patient has not yet experienced an infection. Replacement immunoglobulin infusions should be considered also in patients with immunoglobulin G serum levels $\geq$400 mg/dL if severe, persistent, or recurrent infections occur.

A widely used initial immunoglobulin replacement dose is 400-500 mg/kg. Subsequent dosing should be repeated every 3-4 weeks until evidence of recovery of the humoral arm of the immunity. A diffuse clinical practice for conferring protection against infections, in particular of bacterial origin, is that of maintaining the immunoglobulin G serum levels above 400 mg/dL. Robust guidance on stopping immunoglobulin replacement therapy is lacking. Hypogammaglobulinemia secondary to B-cell depleting therapy is usually reversible; thus, periodic reassessment and a monitored trial off therapy are reasonable. Immunoglobulin replacement should continue until immunoglobulin G serum levels remain greater than 400 mg/dL unsupported by immunoglobulin replacement over 2 consecutive months. Decision to discontinue replacement therapy should also be guided by taking into consideration the changes in serum levels of immunoglobulin M and A, since their value is not affected by replacement therapy and, therefore, increases in immunoglobulin M and A serum levels can provide insight into the progress of immune reconstitution after completion of B-cell-depleting therapies. In this respect, it has also to be highlighted that since immunoglobulin A and M are not corrected through substitutive therapy, infusion of immunoglobulin G does not completely compensate for the overall impaired immunoglobulin production, which can at least partly contribute to the risk of infections even in patients receiving immunoglobulin replacement.

When describing the evidence, the adult 20-mg and pediatric 5-mg/m², maximum 20-mg, dexamethasone regimens should be characterized as protocol-derived and not objectively documented in prospective clinical trials. The data informing differences in US label and EU labels, as well as adult and pediatric patients, should be reported.

Dexamethasone pre-medication should be restricted to administration before the 1st cycle of treatment with blinatumomab. As mentioned above, before the 1st blinatumomab cycle, the administration of dexamethasone is justified for the prevention of first dose reactions such as allergy since blinatumomab is a murine molecule. There is no proof that the administration of dexamethasone has any benefit for patients beyond cycle 1. Future prospective studies and information deriving from structured registries should also address the key point of identifying the recommended corticosteroid doses. A dexamethasone dose-de-escalation or non-inferiority study could determine whether lower doses provide equivalent protection from first dose effects.

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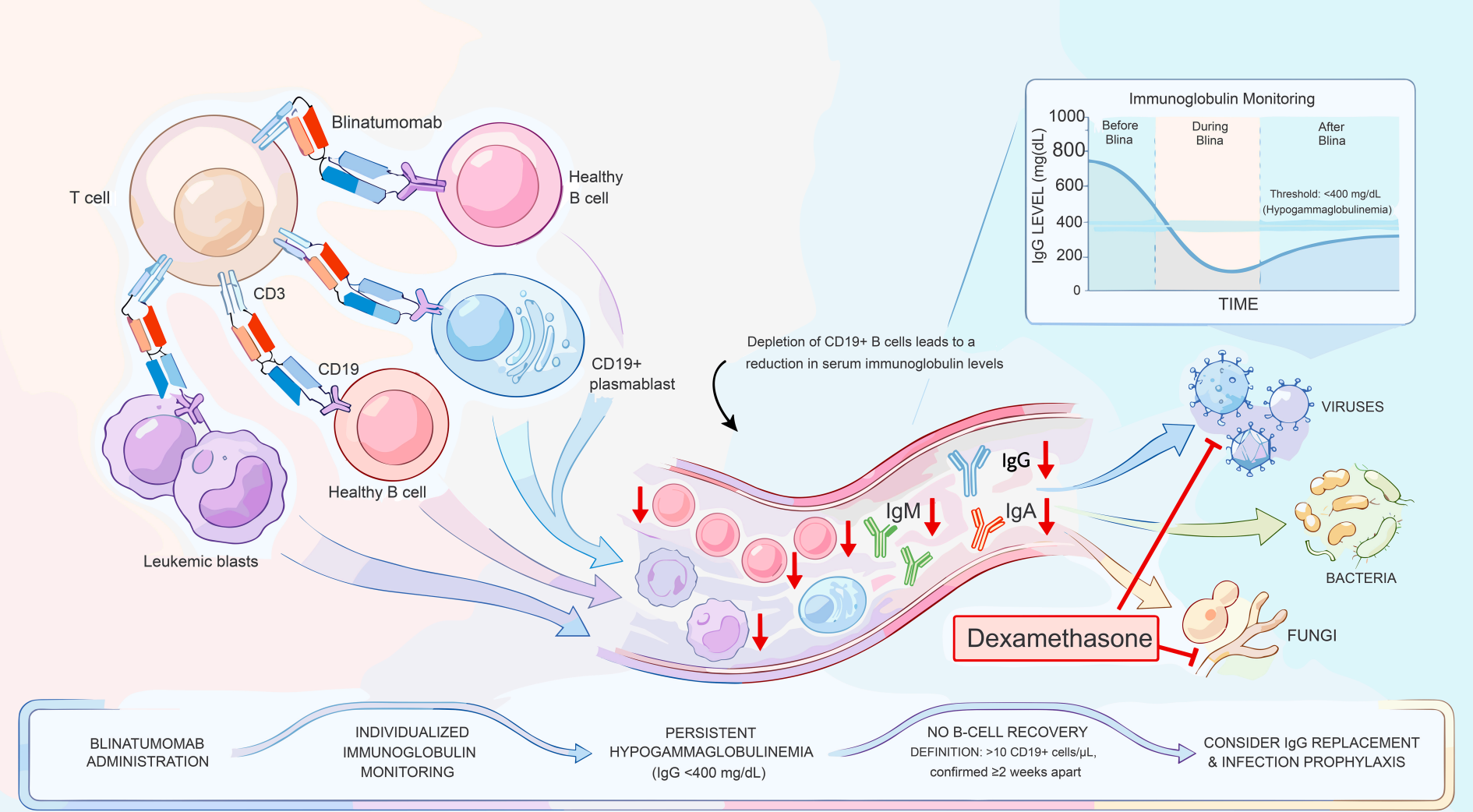
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Figure 1 legend: Effect of blinatumomab on normal B lymphocytes and plasma-blasts, as well as of impaired immunoglobulin production. Influence of dexamethasone on increased risk of infections.


Blinatumomab
T cell
Healthy
B cell
CD3
CD19
CD19+
plasmablast
Healthy B cell
Leukemic blasts
Depletion of CD19+ B cells leads to a
reduction in serum immunoglobulin levels
Immunoglobulin Monitoring
IgG LEVEL (mg/dL)
1000
800
600
400
200
0
Before
Blina
During
Blina
After
Blina
Threshold: <400 mg/dL
(Hypogammaglobulinemia)
TIME
IgG
IgM
IgA
VIRUSES
BACTERIA
FUNGI
Dexamethasone
BLINATUMOMAB
ADMINISTRATION
INDIVIDUALIZED
IMMUNOGLOBULIN
MONITORING
PERSISTENT
HYPOGAMMAGLOBULINEMIA
(IgG <400 mg/dL)
NO B-CELL RECOVERY
DEFINITION: >10 CD19+ cells/μL,
confirmed ≥2 weeks apart
CONSIDER IgG REPLACEMENT
& INFECTION PROPHYLAXIS