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APLASTIC ANAEMIA ASSOCIATED WITH BENDAMUSTINE THERAPY – A RARE SIDE EFFECT

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ABSTRACT

Introduction: During treatment for malignant lymphoma, cytopenia can develop for several reasons. This can range from mild cytopenias leading to infection and bleeding to full-blown drug-induced aplastic anaemia. While aplastic anaemia affects individuals of all genders and ages, here, we describe aplastic anaemia after chemotherapy exposure to bendamustine in a 65-year-old female with non-Hodgkin's lymphoma.

Case description: A 65-year-old woman with recurrent indolent marginal zone lymphoma and post-chemotherapy with bendamustine and rituximab, presented with a neutropenic fever and was admitted with a leading diagnosis of sepsis. In the previous two weeks, the patient required regular transfusions of packed red blood cells and platelets and maintained a daily ZARXIO® regimen. Laboratory results revealed pancytopenia, and broad-spectrum antibiotics (cefepime/vancomycin) were given. The patient was subsequently admitted to the hospital under the care of the haematology/oncology team and was ultimately diagnosed with aplastic anaemia, likely as a consequence of bendamustine chemoimmunotherapy. She elicited a positive response to the triple immunosuppressive therapy (IST) regimen (two immunotherapeutic agents plus one anti-thymocyte globulin (ATG), after which her cell counts returned to normal.

Conclusions: This case underscores the importance of recognising haematologic complications linked to bendamustine and advocates for further research to increase the understanding among healthcare professionals of drug-induced aplastic anaemia. Bendamustine can cause severe autoimmune haemolytic anaemia and aplastic anaemia and may require multiple transfusions and a multidrug regimen for treatment. The use of ATG as a therapeutic intervention is appropriate because it has been effective in treating aplastic anaemia.

KEYWORDS

Bendamustine, drug-induced aplastic anaemia, anaemia, non-Hodgkin's lymphoma, pancytopenia

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LEARNING POINTS

- Bendamustine can cause severe autoimmune haemolytic anaemia and aplastic anaemia, a side effect which has rarely been reported but is of significant clinical importance.
- Drug-induced aplastic anaemia is a complex, potentially devastating consequence of treating blood cancers and is a relatively unexplored area that requires further understanding.
- Anti-thymocyte globulin is effective in treating bendamustine-induced aplastic anaemia as it degrades lymphocytes that destroy the bone marrow.

INTRODUCTION

Bendamustine, a bifunctional alkylating agent with both alkylating and antimetabolite moieties in its unique chemical structure, provides a pertinent example within the context of drug-induced aplastic anaemia. While the mechanism of action of bendamustine involves the formation of DNA adducts, leading to the inhibition of DNA replication and repair, it also induces DNA strand breaks, triggering apoptosis in rapidly dividing cells, including haematopoietic precursors. This dual mechanism sets bendamustine apart from other alkylating agents, making it effective in treating various malignancies. It is also indicated for specific subtypes of non-Hodgkin's lymphoma, encompassing both indolent and aggressive forms, either as a single agent or in combination with rituximab. During treatment for malignant lymphoma, cytopenia can develop for several reasons. Drug-induced aplastic anaemia is a complex, potentially devastating consequence of treating blood cancers and is a relatively unexplored area that requires further understanding. Aplastic anaemia is a haematologic disorder characterised by bone marrow failure, resulting in reduced or absent haematopoietic precursor cells. The emergence of drug-induced aplastic anaemia highlights the intricate relationship between external substances and the delicate balance of haematopoiesis. While many medications effectively treat various medical conditions, an increasing number of these treatments have been linked to the development of aplastic anaemia. Examples of these agents include chloramphenicol, antiepileptic drugs, thiazides, amidopyrine and trimethoprim/ sulfamethoxazole. The exact mechanisms underlying the pathophysiology of drug-induced aplastic anaemia are unclear, but a widely accepted theory suggests an abnormal immune response. According to this theory, a malfunctioning immune system activates autoreactive T cells, leading to the targeted destruction of haematopoietic stem and progenitor cells in individuals genetically predisposed to susceptibility[1]. However, bendamustine can cause myelosuppression, leading to conditions such as neutropenia, thrombocytopenia, and anaemia. While there is limited scientific evidence linking bendamustine to aplastic anaemia as a side effect, we present the case of a 65-year-old female who developed this condition a few weeks after starting bendamustine/rituximab treatment for her second relapse of non-Hodgkin's lymphoma. She was found to have pancytopenia and neutropenia following laboratory work, with associated fevers.

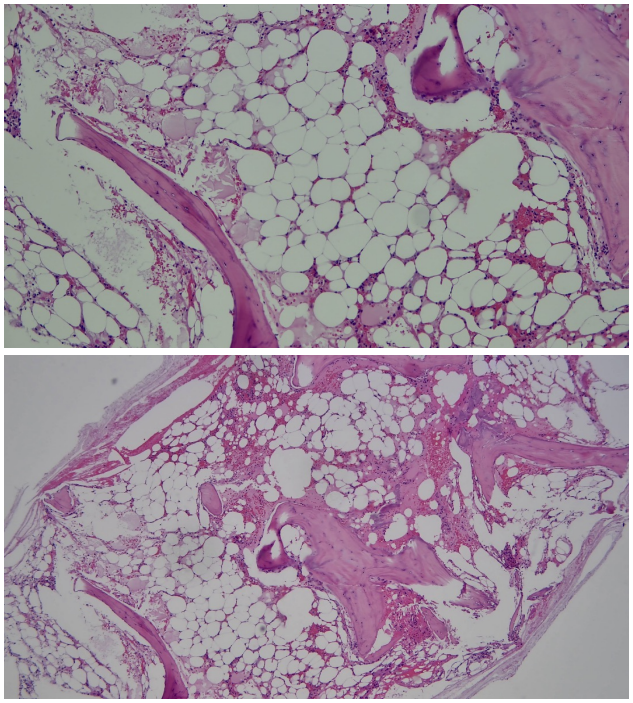

Figure 1. Hypocellular bone marrow with rare, scattered lymphocytes and erythroid precursors. No atypical lymphoid aggregates could be seen.

CASE DESCRIPTION

A 65-year-old woman with a history of recurrent indolent marginal zone lymphoma and post-chemotherapy with bendamustine (90 mg/m^2) and rituximab (×1 on 23 September 2023) presented to the emergency department, sent by her oncologist's outpatient office, after experiencing a measured temperature of 38.6°C. Despite taking paracetamol, her temperature increased to 39.1°C. She denied any other symptoms or recent contact with anyone who was sick. In the previous two weeks, the patient required regular transfusions of packed red blood cells and platelets, and she maintained a daily ZARXIO® regimen.

Upon admission, her laboratory test results showed low levels of blood cells and neutrophils *(Table 1)*. She was given broad-spectrum antibiotics (cefepime/vancomycin) and was admitted to the hospital under the care of the haematology/oncology team. Tests for urinary tract infection and respiratory viral pathogens were negative, but blood cultures confirmed the presence of *Escherichia coli*

bacteraemia. Subsequently, an image-guided bone marrow biopsy was performed, which did not reveal evidence of lymphoma but showed findings consistent with aplastic anaemia. The marrow lacked cells (hypocellular/aplastic, with approximately 5% cellularity) in all three blood cell lineages, with only a few scattered lymphocytes and erythroid precursors present *(Fig. 1)*.

Flow cytometry analysis revealed a decrease in marrow components, with B cells either absent or present in very low numbers. There was no evidence, either morphologically or immunophenotypically, to suggest the presence of B-cell lymphoma. Cytogenetic analysis of 20 cells revealed that two of these cells had an extra copy of the X chromosome, resulting in a karyotype of 47, XX, +X[2]/46, XX[18]. The remaining cells had a seemingly normal karyotype, and no other consistent numerical or structural chromosome abnormalities were detected using the technology employed in this analysis. Fluorescent in situ hybridisation studies showed normal results.

The etiology of patient's aplastic anemia remains unclear. It could be a consequence of the bendamustine treatment, or it could be directly linked to her primary diagnosis of marginal zone lymphoma.

	On admission	Reference Range
WBC	0.23 K/µl	4.8–10.8 K/µl
RBC	2.42 M/µl	4.2–5.4 M/µl
Hgb	7.1 g/dl	12–16 g/dl
HCT	20.4%	37–47%
MCV	84.3 fl	81–99 fl
MCH	29.3 pg	27–31 pg
Platelets	31 K/µl	130–400 K/µl
Neutrophil count	0.00 K/µl	1.4–6.5 K/µl

Abbreviations: WBC, white blood cells; RBC, red blood cells; Hgb, haemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin;

Table 1. Patient laboratory results.

DISCUSSION

In the field of chronic lymphocytic leukaemia (CLL) treatment, bendamustine has emerged as a notable chemotherapeutic agent. The agent is now globally available for treating various conditions, such as CLL, indolent and aggressive B NHL, and T NHL and HL, multiple myeloma, and even breast cancer[2]. However, there is a delicate balance between the therapeutic effects and the haematological and non-haematological side effects of such medications, some of which can lead to severe conditions such as aplastic anaemia. Bendamustine is a mechlorethamine derivative that is structurally similar to chlorambucil[2]. In a drug trial performed by Knauf et al. in 2009, bendamustine demonstrated significantly greater efficacy than chlorambucil and a manageable toxicity profile when used as a first-line therapy for advanced CLL patients[3]. However, 8% of bendamustine-treated patients experienced severe infections[3].

This report highlights a rare but serious side effect associated with bendamustine therapy – aplastic anaemia. The most common adverse events experienced by patients receiving bendamustine are haematological events and gastrointestinal disturbances. The primary dose-limiting toxicity is haematologic in nature[2]. Researchers are currently investigating various questions regarding the optimisation of bendamustine therapy, such as determining the appropriate dose and schedule, understanding its role compared to other available treatments and managing its toxicity. After reviewing the literature, we found very few cases of aplastic anaemia caused by bendamustine. For example, Nagashima et al. (2016) reported a case of severe pancytopenia in a patient who underwent rituximab and bendamustine therapy for a second relapse of diffuse large B-cell lymphoma[4]. Another paper described a case of haemolytic anaemia resulting from bendamustine exposure, which was successfully treated with prednisolone[5]. In a clinical trial conducted by Ghilardi et al. (2022), compared to patients receiving fludarabine/cyclophosphamide, patients in the bendamustine group experienced side effects such as neutropenic fever and hospitalisation after infusion. However, the bendamustine group had lower rates of cytokine release syndrome and neurotoxicity[6]. Also, there have been reports of treatment-related infections, such as fatigue, nausea, dry mouth and fever[2].

The development of aplastic anaemia in our patient following bendamustine treatment raised critical considerations regarding the haematological safety profile of the drug. This condition is hypothesised to stem from an abnormal response leading to the destruction of bone marrow stem cells, a side effect not widely reported but of significant clinical importance. Although there are guidelines available for the treatment of drug-induced immune haemolytic anaemia (which involves discontinuing the causative drug and providing supportive care)[7], there is limited data on the treatment of bendamustine-induced aplastic anaemia. The use of ATG as a therapeutic intervention is appropriate because it has been effective in treating aplastic anaemia. The immunosuppressive action of ATG targets lymphocytes, which are involved in the autoimmune aspect of marrow destruction, thus promoting marrow regeneration. The effectiveness of steroids in this context is uncertain, as it is challenging to differentiate their benefits from those of stopping the drug[17].

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