usually accompanied by regular maturation and is a result of iron dysregulation, renal insufficiency, or marrow replacement in cases of higher infiltration of atypical plasma cells. This is in contrast to the common concept of predominantly T-cell-driven PRCA pathomechanisms [12]. The study by Korde *et al.* [12] also provided data on the treatment of eight patients with monoclonal gammopathy and PRCA. All patients were refractory to immunosuppressive therapies such as cyclosporin A, rituximab, and corticosteroids. Six patients showed no response to daclizumab, an antibody for idiopathic PRCA. In three patients, anti-myeloma therapy (lenalidomide and bortezomib) led to remission with transfusion independence [12].

In conclusion, the diagnosis of T-LGL leukemia is based on immunocytological and cytomorphological investigations. Subsequent molecular genetic analyses are important for confirming the diagnosis of T-cell neoplasias based on T-cell receptor clonality. PRCA is a serious complication of T-LGL leukemia.

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Ibrutinib combined with gemcitabine-vinorelbine for primary refractory non-Hodgkin lymphoma

TO THE EDITOR: Refractoriness to primary treatment is a problematic issue in DLBCL (diffuse large B-cell lymphoma) and failure to respond to salvage regimens also renders patients ineligible for autologous SCT (stem cell transplantation) [1, 2]. Additionally, the ABC (activated B-cell-like) phenotype yields poor results with standard chemoimmunotherapies; thus, it is recommended that novel agents, such as ibrutinib and lenalidomide, be incorporated into the treatment regimen [3]. The effectiveness of the single-agent use of ibrutinib in relapsed/refractory DLBCL, especially in the ABC phenotype, has been previously demonstrated, mainly in early phase clinical studies [4]. Furthermore, combination studies of ibrutinib with novel agents have shown efficacy in treating DLBCL, including transformed DLBCL [5-7].

Combination studies of ibrutinib with chemotherapy regimens such as R-DA-EPOCH (rituximab and dose-adjusted etoposide, vincristine, cyclophosphamide, and adriamycin) [8], gemcitabine-cisplatin-rituximab [9], RB (rituximab-bendamustine) [10, 11], and R-ICE (rituximab ifosfamide, carboplatin, etoposide) [12], appear to be effective and safe in early-phase studies. Gemcitabine-vinorelbine is an old and effective chemotherapy regimen for DLBCL [13]. In this study, we retrospectively evaluated the demographic and clinicopathological data of patients with non-Hodgkin's lymphoma who received IGV (ibrutinib in combination with gemcitabine-vinorelbine) chemotherapy at our center.

The regimen was administered off-label but with the approval of the national health authorities on a patient-by-patient basis and with the consent of the patients. This study was approved by the local ethics committee of the Ankara Bilkent City Hospital (E1-23-3783, 07.2023). Informed consent was not required because the study reported retrospective observational data.

IGV treatment was administered to six patients. The age of the patients was 45.8±21.59 (median±SD) years, and the female to male ratio was 2:4. Among these patients, one had hypothyroidism, one had rheumatoid arthritis, and one had hypertension.

Among the six patients who received IGV treatment, five had DLBCL. In this group, the cell of origin was germinal center B-cell-like in one patient and ABC phenotype in four patients. Two patients with the ABC phenotype DLBCL received IGV and were diagnosed with RT (Richter's transformation) from CLL (chronic lymphocytic leukemia). Two patients had bone marrow involvement at diagnosis, but none had CNS (central nervous system) involvement. The median IPI (international prognostic index) score was 3 (range, 2–4). Although BCL-2 and BCL-6 were positive in four patients, the MYC expression status could not be evaluated due to unavailability at our center. Before IGV administration, three patients had stage 4 disease, one had stage 2E disease, and one had stage 3 disease. None of these patients had bone marrow or CNS involvement before IGV administration. Additionally, one patient had follicular lymphoma grade 3B, and her follicular lymphoma international prognostic index score was 2. No bone marrow or CNS involvement was observed at the time of diagnosis or before IGV administration. The clinical characteristics and survival data are summarized in Table 1. Progression-free survival is defined as the time from IGV initiation to disease progression or death from any cause. Time to the next treatment (the time from IGV initiation to the initiation of salvage treatment) is given for Patient 5, who received salvage treatment despite having a stable disease response to IGV.

While a complex karyotype was observed at diagnosis in a patient with RT, no cytogenetic abnormalities were observed in other patients at diagnosis or before IGV treatment. FISH (fluorescence in situ hybridization) analysis results were negative for the CLL panel [*del17p, t(14:14), trisomy/monosomy 12, del13q, del11q22*] before IGV treatment in the patient with complex karyotype. FISH analysis was not performed for other patients. Molecular tests were not performed for any of the patients.

IGV was administered to patients after receiving ≥3 lines of treatment. All patients were refractory to first-line R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy. Second- and third-line chemotherapies are rituximab, dexamethasone, cisplatin, and cytarabine and R-DA-EPOCH (most commonly), followed by R-ICE, RB, and R-CVP (rituximab, cyclophosphamide, vincristine, and prednisolone). RB and R-CVP were preferred for elderly patients who were unsuitable for intensive treatment.

IGV was administered for a median of 3 cycles (range, 3–5). The treatment schedule included gemcitabine (1,000 mg/m^2, intravenously on days 1 and 8), vinorelbine (25 mg/m^2, intravenously on days 1 and 8) every 21–28 days, and continuous oral ibrutinib 560 mg/day. In one patient who was not suitable for intensive treatment, IGV was administered with a 50% dose reduction of gemcitabine and vinorelbine. No abnormalities were observed in the patient's liver and kidney functions before treatment.

After 3 cycles, there was one CR (complete response), one PR (partial response), one stable disease, and three progressions. IGV was discontinued in all the patients. The reasons for discontinuation were the need to proceed to SCT (four patients) and unresponsiveness (two patients).

Among the four patients whose IGV treatment was discontinued for SCT, autologous SCT was performed in one patient with a CR and two patients with progression. Autologous SCT was administered to one patient whose IGV treatment was discontinued because of a lack of response, following the rituximab-lenalidomide-bendamustine salvage therapy with a partial response. Two of the four patients who underwent autologous SCT are still in remission. Haploidentical allogeneic SCT was performed in one patient with PR. However, this patient experienced a relapse on the 71st day after transplantation and died

Table 1. Clinical characteristics of the patients.

	Age	Sex	Stage	LDH	Extranodal involvement	ECOG score	PFS (mo)	OS (mo)
Patient 1	38	Male	2E	Above normal range	Yes	0	4.9	22
Patient 2	41	Male	4	Above normal range	Yes	0	8.2	9.2
Patient 3	61	Female	4B	Above normal range	Yes	1	5.8	14.9
Patient 4	20	Male	4BX	Above normal range	Yes	0	2.4	21.1
Patient 5	51	Male	4E	Above normal range	Yes	0	2.3[a)]	20.3
Patient 6	83	Female	4BS	Normal	Yes	2	2.5	2.7

[a)]Time to the next treatment (refer to the text).
Abbreviations: ECOG, eastern cooperative oncology group; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

Table 2. Adverse events during treatment[a].

	Grade 1–2	Grade 3–4
Non-hematological toxicity (N of patients)		
Adenoviral conjunctivitis	1	-
Sensorimotor polyneuropathy	1	-
Hepatic transaminase elevation	-	1
Hematological toxicity (N of patients)		
Anemia	2	-
Neutropenia	-	6
Thrombocytopenia	2	3

[a]According to the Common Terminology Criteria for Adverse Events version 5.0.

on the 101st day. One patient who relapsed after autologous SCT underwent HLA-matched sibling donor allogeneic SCT and remained alive. The overall survival after IGV in all patients was 17.6±7.71 months (median±SD). Adverse events during treatment are detailed in Table 2.

Our theoretical idea that the combination of a targeted therapy with chemotherapy would show synergistic activity and the fact that the patients are refractory to various chemo-immunotherapy regimens other than gemcitabine-vinorelbine, led us to try IGV in this cohort. The first patient to whom this regimen was administered was refractory to three lines of treatment and showed a partial response to IGV, allowing us to proceed with allogeneic SCT. In the second patient, who was also refractory to three lines of treatment, IGV served as a bridge to autologous SCT with CR. Although these two patients relapsed after SCT, their initial responses were promising regarding the effectiveness of the treatment. However, the desired response was not observed in other patients. Although no response to IGV was observed, ongoing responses were achieved with autologous SCT in two patients. This cohort was too small to determine which patients would or would not respond to IGV. Moreover, the responses to be obtained when applied in earlier lines, in chemosensitive relapses, or as the first line of treatment in elderly patients, are not yet clear.

We can state that hematological adverse effects are common with IGV, but they are generally easily manageable. Although non-hematological adverse effects occur during IGV administration, whether they are caused by this treatment is not confirmed yet. They may possibly be related to previous chemotherapies or to the disease itself. In the patient with elevated hepatic transaminase levels, viral and autoimmune causes were excluded through serological and molecular workup. Stem cell mobilization was successful in four patients; therefore, IGV is probably a reliable regimen in terms of stem cell toxicity. Further clinical studies are required to obtain definitive answers to these questions.

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Successful recovery of poor graft function by administration of romiplostim in a multiple myeloma case with poor graft function following autologous stem cell transplantation

TO THE EDITOR: Despite advances in treatment options, including the use of novel agents, such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, autologous hematopoietic stem cell transplantation (auto-HSCT) remains the cornerstone of treatment of multiple myeloma (MM) [1]. Following marrow suppression by high-dose chemotherapy as a prelude to auto-HSCT, most patients achieve hematopoietic recovery after autologous stem cell infusion. However, some patients unexpectedly develop poor graft function (PGF). Although there is no universally accepted definition of PGF after auto-HSCT, the European Society for Blood and Marrow Transplantation (EBMT) guidelines suggest defining PGF as two or three cytopenia lasting for at least 2 weeks, 28 days after hematopoietic stem cell transplantation [2]. In a recent prospective study, PGF was defined as sustained cytopenia, defined as platelet count ≤50,000/μL, and/or hemoglobin ≤8 g/dL, and/or absolute neutrophil count (ANC) ≤ 1,000/μL [3].

PGF broadly encompasses several rare disease conditions that are characterized by continued requirements for blood transfusions or an increased risk of infection due to neutropenia, such as post-transplantation immune thrombocytopenia purpura (ITP) or bone marrow aplasia [4, 5]. Therefore, persistent PGF can negatively impact the quality of life after auto-HSCT. Moreover, it may limit subsequent treatments, such as maintenance or consolidation therapies, and adversely affect disease control. Despite these potential consequences, no systematic approach for diagnosing and managing PGF is known currently.

Thrombopoietin (TPO) receptor agonists (TPO-RAs) enhance the production of hematopoietic stem cells and megakaryocytes by stimulating the TPO receptor, also known as myeloproliferative leukemia protein. Two TPO-RAs, eltrombopag and romiplostim, have been approved by the Food and Drug Administration to treat cytopenia in conditions, such as ITP and aplastic anemia [6, 7]. Owing to their mechanism of action of stimulating hematopoietic stem cell production, TPO-RAs are currently being explored for the treatment of PGF following auto-HSCT [5]. However, the existing reports have primarily provided descriptive information, often involving small cohorts. Moreover, studies of post-transplantation PGF have predominantly focused on allogeneic hematopoietic stem cell transplantation.

In this report, we present the case of a patient with MM who successfully recovered from PGF following auto-HSCT by treating with romiplostim. This recovery was achieved even after the initial TPO-RA (eltrombopag) was ineffective. This study was approved by the Institutional Review Board of the Catholic University of Korea (KC22 RISI0540) and was conducted in accordance with the Declaration of Helsinki.

CASE

A 62-year-old woman was diagnosed with transplant-eligible MM. The patient underwent a predetermined therapeutic approach, which included six cycles of induction chemotherapy followed by auto-HSCT. The induction chemotherapy regimen consisted of bortezomib, thalidomide, and dexamethasone. She achieved complete response at 15 weeks after initiation of the therapeutic approach. Bone marrow biopsy before auto-HSCT revealed stringent CR (Fig. 1D). To prepare auto-HSCT, stem cells were mobilized using 10 μg/kg/d of G-CSF for 5 days and of 375 mg/m^2 of etoposide for 1 d. For pretreatment with auto-HSCT, the patient received 3.2 mg/kg/d busulfan for 3 days and 200 mg/m^2/d thiotepa for 2 days [8]. Subsequently, CD34+ cells at a dose of 4.02×10^6/kg were infused for auto-HSCT. No post auto-HSCT maintenance or consolidation treatments were administered. The patient remained free of clinically significant adverse events for 9 months after auto-HSCT.

At 285 days post-auto-HSCT, the patient's platelet count unexpectedly dropped to 5×10^9/L, while hemoglobin concentration remained at 11.4 g/dL, and the absolute neutrophil count (ANC) was 1.08×10^9/L, which was within a clinically nonsignificant range (Fig. 2). We were unable to identify any potential causes of thrombocytopenia, such as graft failure, MM progression, secondary myeloid neoplasm, infection, or toxic drug effects. The diagnosis that we arrived at was post-auto-HSCT PGF, supported by a bone marrow study that revealed 15% cellularity without cytogenetic abnormalities, malignant cancer cells, fibrosis, or dysplastic changes (Fig. 1G). Considering the prominence of thrombocytopenia within the spectrum of PGF, we initiated treatment with oral dexamethasone (40 mg/d for 4 d) and intravenous immunoglobulin (1 g/kg/d for 2 d) following therapeutic indications for ITP [9]. Regrettably, these interventions resulted in further neutropenia (0.65×10^9/L), and no platelet recovery (22×10^9/L) was observed 189 days after the initiation of high-dose dexamethasone and intravenous immunoglobulin. Consequently, we revised the diag-