

Daratumumab and Romiplostim Combined Therapy for a Long-Standing Refractory Primary Immune Thrombocytopenia – Case Report

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Abstract: Multi-refractory immune thrombocytopenia (ITP) is not uncommon and associated with high morbidity and mortality rates. Although the precise mechanism of ITP is not yet fully understood, a therapeutic approach that relies on using a single agent in each treatment line may not be sufficient in this population. We report the case of a 67-year-old female with long-standing multi-refractory ITP treated with a combination of Daratumumab and Romiplostim who achieved a durable response for more than 42 weeks. Owing to the presentation of chronic and refractory disease, we used a dual-agent approach to address early immune destruction and promote megakaryocyte platelet production. Three doses of Daratumumab were administered during the induction phase (weeks 0,1,5) and then at less frequent intervals - every 4–12 weeks for total of 4 doses during the maintenance phase. Romiplostim was administered weekly, with dose modification depending on the platelet count. We hypothesize that when combined with thrombopoietin receptor agonists (TPO-RAs), daratumumab administered at less frequent intervals over an extended period can be safely used, resulting in a prolonged response.

Keywords: multi-refractory immune thrombocytopenia, anti CD38 directed therapy, TPO mimetic agents, case report

Introduction

The incidence of immune thrombocytopenia (ITP) among the adult population is 3.8 cases per 100,000 person-years.¹ Up to 70% of these patients experience a chronic course.² While most patients with chronic ITP do not require further treatment, a refractory course is not uncommon and is associated with higher morbidity and mortality rates.³

Corticosteroids and intravenous immunoglobulin (IVIG) are the primary first-line treatments for ITP, while second-line therapies include splenectomy, anti-CD20 antibody (rituximab), thrombopoietin receptor agonists (TPO-RAs), and the recently FDA-approved Syk inhibitor, fostamatinib. Patients with severe or symptomatic thrombocytopenia that is unresponsive to sequential therapy are considered multi-refractory and typically offered immunosuppressive agents, which, unfortunately, often leads to unsatisfactory long-term results.⁴

The precise mechanism underlying ITP is not fully understood. A conventional theory posits that antibody-coated platelets are prematurely eliminated within the reticuloendothelial system. Other potential mechanisms include T-cell dysregulation, complement-mediated platelet destruction, and immune-mediated inhibition of megakaryocyte platelet production.⁵ An alternative theory proposes that refractory ITP may result from antibody secretion by long-lived plasma cells.^{4,6} This mechanism, which bypasses the targeted CD20-positive B cells, may explain the low response and high recurrence rates observed following rituximab treatment.⁷ Therefore, in this paper, we present the approach of combined therapy including daratumumab, a monoclonal antibody that targets CD38 on plasma cells and the TPO mimetic agent, romiplostim, as an alternative approach for the management of multi-refractory ITP.

Case Presentation

We present the case of a 67-year-old female with multi-refractory ITP who was admitted to our center because of fever, hypoxia, and thrombocytopenia, with a platelet count of $3 \times 10^9/L$. She was diagnosed at the age of 21 and subsequently treated with multiple corticosteroid courses, IVIG, rituximab, TPO-RAs including eltrombopag and romiplostim, cyclosporine, fostamatinib, and a splenectomy, without achieving a significant or sustainable response. She experienced numerous complications due to profound thrombocytopenia, including subconjunctival and subarachnoid hemorrhages, multiple hospitalizations involving extensive corticosteroid use, and recurrent IVIG infusions with and without TPO-RA. Evaluations indicated she was positive for lupus anticoagulant and a bone marrow biopsy revealed several dysplastic changes including increased megakaryocyte number and erythroid megaloblastoid changes, a normal karyotype, and a mutated TET2 (His1945Arg) with a variant allele frequency of 49.3%, suggesting a germline mutation.

In the three months leading up to her hospital admission, her platelet count ranged from 1 to $6 \times 10^9/L$, despite treatment with corticosteroids and IVIG. During her hospital stay, she was diagnosed with bilateral pneumonia and treated with broad-spectrum antibiotics. Following an episode of hemoptysis, a chest computed tomography (CT) scan revealed alveolar hemorrhage. Despite treatment with high-dose corticosteroids, IVIG, romiplostim and platelet infusions, her platelet count remained critically low.

We decided to use daratumumab as an “off-label” treatment, delivered subcutaneously at a fixed dose of 1800 mg, in combination with romiplostim at a maximal weekly dose of 750 mcg (10 mcg/kg). Premedication with dexamethasone (10 mg) was administered intravenously prior to each daratumumab administration. Our patient provided informed consent after being apprised of the nature of treatment and its potential side effects. Two induction doses of daratumumab were administered subcutaneously within a week, followed by subsequent treatments, as deemed necessary, in the event of a platelet count dropping below $30 \times 10^9/L$. Remarkably, within 22 days of commencing the daratumumab treatment, her platelet count increased to $205 \times 10^9/L$. However, in week 5, the patient experienced a relapse, with the platelet count dropping to $22 \times 10^9/L$, leading to the administration of a third dose of daratumumab. During follow-up, we noticed a significant drop in the platelet count at weeks 15, 22, 26, and 37, prompting the re-administration of daratumumab. Follow-up period presented in this paper is 12 months since initial intervention. The patient gave informed consent for case publication. Our institutional policy does not require any additional institutional ethics approval.

We report a sustained response in a patient with chronic multi-refractory ITP following subcutaneous daratumumab treatment, representing a novel targeted immunotherapy after failure of numerous approved lines of therapy. Initially, our patient received three doses of SC Daratumumab at weeks 0, 1, and 5. Subsequently, we adopted a count-adapted approach for maintenance, necessitating the administration of 4 additional doses. Following the initial induction phase, we observed three episodes of a rapid decrease in PLT count at intervals of 4–10 weeks apart which responded quickly to the re-administration of daratumumab (Figure 1). As mentioned previously, in addition to daratumumab, our patient also received romiplostim with dose modification depending on the platelet count. The romiplostim dose was reduced to 250 μg when the platelet count approached $500 \times 10^9/L$ and withheld when exceeded it. This combination therapy aimed to address both the induction of megakaryocyte platelet production and reduction of immune-mediated destruction.

Discussion

In line with prior publications regarding the use of daratumumab for immune-mediated diseases and cytopenia, we postulate that targeting long-lived plasma cells can influence the trajectory of multi-refractory ITP resistant to CD20 B-cell targeted therapy and immunosuppressive agents.

Crickx and colleagues⁸ described five cases of ITP treated with 4–7 intravenous daratumumab infusions. Only two patients achieved a sustained response after 3 months. Strüßmann and colleagues⁹ published a case of multi-refractory ITP treated with a total of 12 infusions of daratumumab, which resulted in long-term remission for at least 20 months. Vernava and Schmitt also reported one of two patients with refractory ITP achieved a durable response using daratumumab as a targeted therapy.¹⁰ The use of daratumumab as a treatment for refractory autoimmune hemolytic anemia has been documented.^{11,12} Its successful use has also been described in post-transplant patients with immune-mediated cytopenia, encompassing thrombocytopenia, hemolytic anemia, and Evan’s syndrome.^{13–15} Furthermore, Jana van den Berg and colleagues¹⁶ treated two patients with refractory immune thrombotic thrombocytopenic purpura (iTTP) with daratumumab, leading to rapid disappearance of

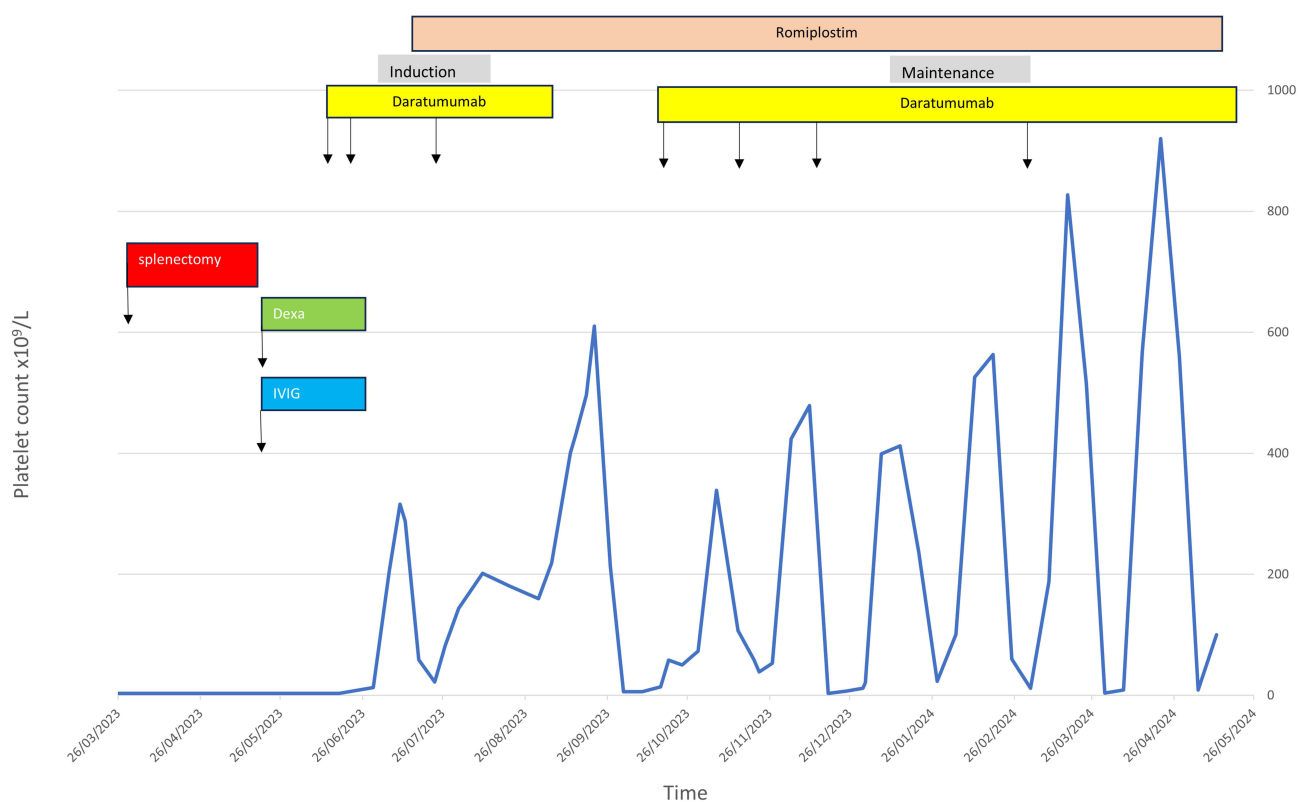


Figure 1 Temporal Changes of Platelet count and type of intervention.

ADAMTS13 autoantibodies and normalization of its activity. Recently, a Phase 1–2 trial reported promising results in the treatment of refractory ITP using a novel anti-CD38 monoclonal antibody.¹⁷

Myelodysplastic syndrome could have been suggested as an alternative diagnosis, although it is highly unlikely due to the relapsing-remitting pattern and early presentation at the age of 16. Notably, the presence of TET2 mutations has been reported in ITP patients and does not exclude the diagnosis of ITP,¹⁸ while it is also linked to a pro-inflammatory state and immune dysregulation.¹⁹ Furthermore, the rapid onset of response cannot be attributed to premedication with dexamethasone, which can be explained by disease refractoriness to higher corticosteroid doses prior to daratumumab administration. The gamma-globulin level at the last follow-up was <300 gr/dl, which was attributed to daratumumab treatment.

Our experience with the use of daratumumab differs from those of previous reports in several respects. Notably, we administered only three doses of SC Daratumumab for “induction” compared with 4–7 in previous reports, with the addition of extended yet less frequent doses for “maintenance”. We deemed this approach more suitable for treating chronic long-standing multi-refractory ITP, as our aim was to sustain prolonged inhibition of long-lived antibody-secreting plasma cells. We assume that intensive induction regimen, adopted in previous reports, is extrapolated from the common practice with rituximab treatment in refractory ITP, which may have a limited effect in maintaining long-term response. In contrast, we observed that a more extended regimen is particularly reasonable, especially in the case of chronic long-standing ITP, compared with severe acute cases. Interestingly, the platelet count peaked to a higher level as treatment progressed, requiring dose modification of romiplostim and longer intervals between daratumumab administration. This observation supports our assumption that a combined approach may be more suitable for long-standing multi-refractory cases.

To the best of our knowledge, this report represents the first documented use of daratumumab combined with TPO-RA for refractory ITP. This treatment approach was chosen to address both mechanisms involved in the pathogenesis of the disease: inhibition of early immune destruction and promotion of megakaryocyte platelet production. TPO-RA may also exert a beneficial immune effect by reducing anti-platelet antibodies.²⁰ It was clear from patient’s medical history that the degree of platelet destruction exceeded the effect of TPO-RA on platelet production. Hereby, the use of daratumumab, which likely decreased the titer of antibodies causing platelet destruction, enabled the beneficial effect of romiplostim.

The study is limited by its single-patient focus, lack of a control group, and relatively short follow-up period. The off-label use of daratumumab and the experimental dosing regimen complicate the generalization of the findings. Additionally, while the therapeutic approach showed durable response, potential long-term side effects and the exact mechanisms behind the treatment's efficacy remain uncertain.

Conclusion

Incorporation of Daratumumab with Romiplostim resulted in a rapid and sustained response in a patient with multi-refractory ITP. We hypothesize that when combined with TPO-RAs, daratumumab administered at less frequent intervals over an extended period can be safely used, resulting in a prolonged response. Further research is warranted to assess the long-term efficacy and safety of plasma cell depletion-directed therapy combined with TPO-RAs in patients with ITP.

Disclosure

The author(s) report no conflicts of interest in this work.

Consent

The patient gave written and informed consent for data publishing.

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