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CASE REPORT

Refractory immune thrombocytopenia. Successful treatment with repeated cyclosporine A: two case reports

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Key Clinical Message

Treatment of chronic, severe refractory immune thrombocytopenia after splenectomy is difficult. Only less data exist on clinical use of cyclosporine A (CyA) in the management of refractory ITP. In this report, we describe two cases in which standard immunosuppressive therapy, other immunosuppression including cyclosporine A or splenectomy had no therapeutic effect. Even after splenectomy, recommended procedures were inefficient and critical thrombocytes count persisted. After repeated administration of cyclosporine A which had been ineffective prior to splenectomy; however, both patients achieved long-term complete remission of the ITP. Side effects of CyA were moderate. The presented cases have confirmed the potential therapeutic effect of CyA in refractory post-SE ITP.

Keywords

Cyclosporine, ITP, refractory.

Case Report 1

In 1999, a previously healthy 23-year-old male was diagnosed with acute immune thrombocytopenia (platelets (PLT) 2×10^9/L) accompanied with cutaneous and mucosal bleeding symptoms. Initially, the patient was treated with corticoids (IV methylprednisolone 1 g/day for 5 days, switched to oral prednisone mg/kg per day). For persistent severe thrombocytopenia, high-dose intravenous immunoglobulin (IVIG) (0.4 g/day for 5 days) was simultaneously administered. As the drugs were ineffective and bleeding symptoms persisted, the patient was treated with CyA (18 days at an effective level) and then with danazol. These procedures brought no effects and PLT remained considerably low (2–6 $\times 10^9$/L). Using ^{51}Cr-labeled allogeneic platelet kinetic study, platelet survival was found to be shortened to less than 1 day, with predominant splenic sequestration. Due to massive hematuria unresponsive to therapy, acute SE was performed. After the procedure, PLT count was temporarily increased to ~40–50 $\times 10^9$/L. However, this only lasted for several days. For recurrent severe thrombocytopenia, immunosuppressive therapy was started with IV HD-cyclophosphamide (1800 mg, repeated after 4 weeks). Seven days later, after the second treatment cycle, severe thrombocytopenia persisted and intracerebral hemorrhage occurred in the left frontal region (sized 25 × 25 × 22 mm with perifocal edema), manifested by transient unconsciousness and repeated epileptic grand mal seizures. The complication was conservatively treated with replacement therapy and high doses of methylprednisolone and immunoglobulins, still with no PLT increase. Subsequently, interferon alpha (6 IU subcutaneously every 2 days) was applied. After administration of 5 doses, however, the treatment was discontinued due to prominent adverse effects, namely fever, severe muscle and joint pains, and large hematomas from subcutaneous administration. This was replaced by continuous infusion of vincristine (0.5 mg/day for 4 days) in combination with dexamethasone (12 mg/day intravenously for 4 days). Once again, the approach was not effective. After his condition improved clinically (PLT 10×10^9/L), the patient was discharged and transformed to outpatient care. On discharge, CyA was started again, more or less out of embarrassment. After 1 week of CyA administration, during an out-patient visit, PLT count was surprisingly found to be 63×10^9/L. During subsequent visits, PLT gradually

became normal. For next 3 years, CyA was administered at the same dose (the therapeutic level was maintained). Thereafter, it was very carefully discontinued over 1 year. For 15 years, the patient has been in complete remission. The intracranial hemorrhage let him with only minimal residual motor deficit. The patient's quality of life may now be characterized as very good. Used treatment modalities and development of platelet counts are shown in Figure 1.

Case Report 2

In 2011, a 50-year-old patient with a history of an episode of transient secondary thrombocytopenia since at 30 years of age was diagnosed as Evans syndrome with severe hemolytic anemia and hemoglobin level of 77 g/L with mild thrombocytopenia (100×10^9/L) induced by bilateral pneumonia. Apart from combined antibiotic therapy, prednisone was administered at a daily dose of 1 mg/kg for 3 weeks. The initial treatment led to remission of hemolysis. Despite corticoid therapy at a dose of 0.5 mg/kg, however, thrombocytopenia progressed to 2×10^9/L and was accompanied by skin bleeding symptoms in week 6. Therefore, high-dose IVIG therapy was started (a total of 1.5 g/kg), together with pulses of IV dexamethasone (40 mg for 5 days). This approach did not lead to higher PLT count. Soon after, immunosuppressive treatment was initiated with a mean daily dose of 5 mg of CyA and ensured effective level of the drug. During the time of severe thrombocytopenia, the patient was admitted to the hospital for massive macroscopic hematuria requiring repeated platelet transfusions. Due to failure to achieve response and persistence of very severe thrombocytopenia, eltrombopag was administered. Even the maximum dose of 75 mg did not result to treatment response. Simultaneously, platelet survival was determined with ^{51}Cr-labeled allogeneic platelets and showed extremely shortened survival with increased splenic sequestration. Three months from the diagnosis, SE was performed that increased PLT to more than 30×10^9/L for only a few days. Due to post-SE refractory platelet count, eltrombopag was administered again, together with dexamethasone pulses. Subsequently, patient received four cycles of rituximab (375 mg/m^2) at weekly intervals. However, none of the procedures was effective. The cutaneous and mucosal symptoms persisted and severe bleeding into oral cavity soft tissues required additional hospital admission and platelet replacement. Three months after SE, severe symptomatic thrombocytopenia (6×10^9/L) persisted. Given the exhausted treatment options and good experience with treating the former patient, an attempt was made to restart CyA therapy (400 mg/day), combined with methylprednisolone at 1 mg/kg. After 1 week of administration of this combination, PLT increased to normal level. Corticoid therapy was gradually discontinued over 3 months. After 6 months, CyA doses were reduced and the lower effective level of the drug in serum was maintained. After another 6 months, dose reduction was retained. After 20 months of CyA administration, therapy was slowly discontinued with ITP remission. Six weeks later, remission was still maintained. Used treatment modalities and development of platelet counts are shown in Figure 2.

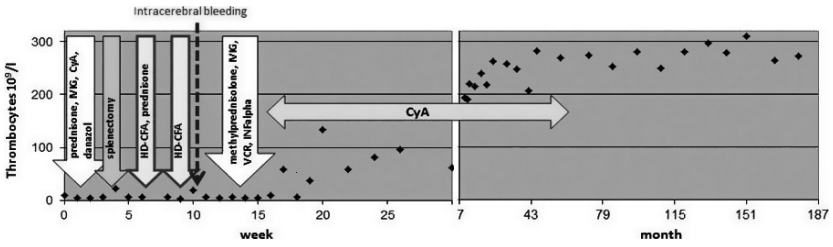

Figure 1. Treatment modalities and development of platelet counts in case 1.

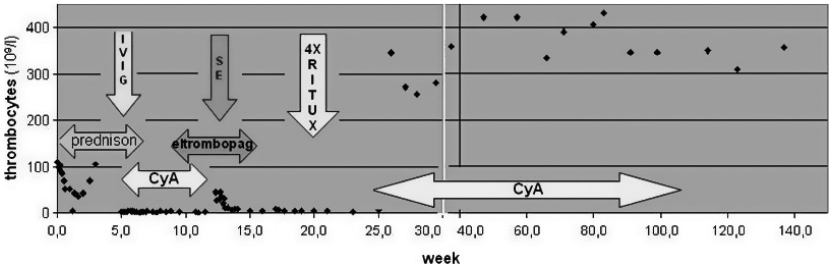

Figure 2. Treatment modalities and development of platelet counts in case 2.

Commentary

Refractory immune thrombocytopenia is a serious clinical problem. For management of these patients, no clearly successful treatment recommendations are available. The definition of refractory ITP has developed over time. For a long time, refractory ITP was defined as a condition of post-SE persistent thrombocytopenia or recurrent severe thrombocytopenia (<20–30 $\times$ 10^9/L), or of higher PLTs but still requiring continued immunosuppressive therapy due to the presence of bleeding symptoms or a high risk for thrombocytopenia progression [1–4]. The incidence of refractory ITP is relatively low. An analysis of six large cohorts of patients initially diagnosed with ITP showed that less than 10% of cases could be labeled as refractory, that is, requiring further therapy after SE [4]. Continued immunosuppressive therapy significantly increases the risk for other, potentially fatal, complications. Rates of death from bleeding complications and complications related to chronic refractory ITP treatment are comparable, being less than 1% of initially diagnosed patients.

More recent immunosuppressive approaches, especially the use of rituximab in ITP therapy, have further improved treatment outcomes and decreased the need for SE. Therefore, some recent definitions include ineffectiveness of this monoclonal antibody in the criteria for chronic refractory ITP. According to some expert recommendations, refractory ITP in adults may be characterized as follows: (1) ITP persisting for >3 months (2) SE and rituximab failure, and (3) PLT <50 $\times$ 10^9/L [5]. The adapted criteria are based on the facts that spontaneous remission of ITP in adults is unlikely after 3 months and that in addition to SE failure, even potentially curative administration of rituximab was not effective. Despite the above clinically significant threshold for moderate thrombocytopenia, further therapy is recommended in lower PLT level, typically <20–30 $\times$ 10^9/L, or if there is a risk for clinically significant bleeding.

New findings in the pathogenesis of ITP, in particular the role of a relative lack of thrombopoietin and inadequate platelet production in the bone marrow contributing to the development of ITP, have led to development of substances overcoming this bone marrow insufficiency. From the second generation of these agents referred to as thrombopoietin mimetics or thrombopoietic receptor agonists (TPO-RAs), two drugs are available for standard clinical use – romiplostim and eltrombopag. In both clinical trials and routine clinical use, the two agents showed good clinical efficacy and safety. Based on these facts, TPO-RAs ware introduced for the treatment of refractory ITP. However, such therapy is not curative and if discontinued, PLTs tend to decrease again [6–9]. According to current recommendations, TPO-RAs should be administered to post-SE patients at a risk of bleeding and if SE is contraindicated and at least one treatment modality fails [10].

For patients who failed even after the above TPO-RA therapy, no clear treatment recommendations are available. In this group of patients, it is crucial to assess the clinical course of ITP with respect to the presence of bleeding symptoms and very frequent effects of immunosuppressive therapy used in the majority of cases. These impair the patients' quality of life and increase both morbidity and mortality associated with the therapy. Therefore, for patients with PLT ≥30 $\times$ 10^9/L and no high risk for bleeding, only observation is clearly recommended [3–5]. In cases of refractory ITP with TPO-RA and rituximab failure, it is advisable to administer first-line drugs (corticosteroids, IVIG or anti-D immunoglobulin) or consider any of the following immunosuppressive modalities: azathioprine, cyclophosphamide, CyA, danazol, dapsone, mycophenolate mofetil, vinblastine or vincristine [11]. For treatment of the most severe symptomatic cases, experimental approaches have been reported in the literature, such as administration of alemtuzumab, combined chemotherapy, and autologous hematopoietic stem cell transplantation.

There is not much experience with CyA in ITP therapy. ording to available data in the literature, this treatment modality has already been tested in patients with a severe form of chronic ITP refractory to other therapies. The published results mostly come from smaller cohorts of patients or case reports. In these studies, CyA was administered as a single drug or in combination with other immunosuppressives.

Cyclosporine A is a strong immunosuppressive. The mechanism of its action, with known etiopathogenesis of ITP, is suppression of both mediated immune reaction and production of antibodies mediated by T cells. CyA suppresses production and release of numerous cytokines including interleukin 2. The above mechanisms have an inhibitory effect on proliferation and differentiation of the autoimmune clone of B cells.

Treatment with CyA led to clinical improvement in up to 80% of patients resistant to initial therapy, with complete treatment response being achieved in more than 40% of patients [12, 13]. In some of the patients, long-term response was maintained even after their therapy was discontinued.

There is more experience with low-dose CyA therapy, either alone or in combination with corticosteroids [12–14]. Combination of CyA with azathioprine and mycophenolate mofetil led to treatment response in 74% [15]. There is limited experience with the use of high-dose CyA. In a group of 14 pediatric patients, treatment response was observed in 50%; of those, four cases showed long-term response [16].

Toxicity of CyA is mostly acceptable; the side effects are mild to moderate and often temporary. Most frequently, they include weakness, arterial hypertension, neuropathy,

dyspepsia, and renal insufficiency. After initiation of therapy, the possible effect may be seen in 3–4 weeks. The initial daily dose is 5 mg/kg for several days; the maintenance dose is ~2.5–3 mg/kg per day. Given the potential side effects, it is recommended to monitor CyA levels and titrate the drug, with levels maintained at 100–200 ng/mL.

We reported two cases of patients with refractory ITP in whom pre-SE therapy with CyA was not effective. Treatment response was not achieved with SE either. As the first patient exhausted treatment options and was at a high risk for bleeding, an attempt was made to restart immunosuppressive therapy with CyA. Surprisingly, this therapy was effective. This experience was analogically applied in the other patients in a similar situation; once again, it was successful. Both patients achieved complete remission of ITP and the response continued after CyA was withdrawn.

The presented cases have confirmed the potential therapeutic effect of CyA in refractory post-SE disease. More interestingly, the immunosuppressive drug was not effective prior to SE. As far as we know, similar observations have not been reported yet.

No reliable explanation for this clinical effect exists. It is likely that there is an interference with autoimmune mechanisms in ITP and these are modified after SE. Another explanation could be the effect of previous immunosuppressive therapy, in particular with rituximab, already available when the latter patient had been treated. It might be interesting to assess retrospectively development of the patients' immune profiles and their changes following immunosuppressive administration, SE, and restart of CyA administration.

Numerous unanswered questions about ITP remain, including the therapeutic approach to patients failing TPO-RA therapy. Our experience suggests a therapeutic potential of CyA. Available data assessing the effectiveness of CyA are not sufficient and comparisons of its effectiveness with other treatment options in ITP are lacking.

Conflict of Interest

None declared.

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