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Editorial

Moving forward with refractoriness

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Management of refractory immune cytopenias, mainly immune thrombocytopenia (ITP) and autoimmune haemolytic anaemia (AIHA) is often challenging to the haematologists due to associated complications such as severe cytopenia related symptoms, drug toxicities and impaired quality of life.

In low economy countries, restricted or non-availability of novel drugs is another major limitation.

In this editorial we discuss the possible therapeutic options available for the treatment of refractory immune cytopenias in our practice based on literature.

ITP versus Refractory ITP

ITP is an immune disorder in which the platelets coated by antiplatelet antibodies are prematurely destroyed by the reticuloendothelial system. There may also be under-production of the platelets contributing to thrombocytopenia[1].

Factors such as dysregulation of T-cells and cytokine networks, genetic and epigenetic risk factors, antibody affinity and specificity, activation of complement, impaired platelet production and alterations in platelet viability and clearance may play a role in refractory ITP[2].

Refractory ITP is defined as the failure to respond to ≥ 2 treatments with no single medication to which they respond while their platelet counts are very low and accompanied by bleeding. In real life, it is simply defined as the persistence of low platelet counts despite the conventional therapies deemed safe for the specific patients regardless of haemorrhagic manifestations[3].

Before establishing the diagnosis of refractory ITP, it is important to revise the diagnosis by excluding alternative diagnoses like myelodysplastic neoplasms (MDS), drug induced thrombocytopenias, inherited thrombocytopenia, bone marrow failure syndromes and type IIB von Willebrand's disease.

Combination therapies, splenectomy and clinical trials are the therapeutic strategies suggested for refractory ITP[3].

Combination therapies

Combination therapies are more effective than single agent therapy in refractory ITP as these target multiple mechanisms related to the pathogenesis concurrently[1]. Evidence on effectiveness of several combinations of conventional therapies are discussed below.

Before the advent of thrombopoietin receptor agonist (TPO-RA), a 50% response rate was achieved with combination therapies like azathioprine with prednisone, mycophenolate mofetil (MMF) with prednisone and cyclophosphamide with prednisone in splenectomized patients. However, the best combination was not identified[3].

A more promising result has been obtained with the combination therapy of TPO-RA (romiplostim or eltrombopag) with an immunosuppressant (MMF or cyclosporin) and intravenous immunoglobulin (IVIg). The study which included 18

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patients who had already failed multiple lines of treatment including splenectomy and TPO-RA alone, demonstrated that satisfactory platelet response (>30,000/ uL or doubling the baseline platelet count after 1 week) was obtained in 72.2%. Majority who responded (11/18), reported only mild side effects like headaches and abdominal pain[4].

The combination of recombinant human thrombopoietin (rh-TPO) and eltrombopag has demonstrated synergistic effect on accelerating platelet production, hence shown to be effective in refractory ITP. This combination induces a rapid onset and durable response with minimum side effects. Two elderly patients aged 76 years and 81 years with refractory ITP, treated with this combination have shown to achieve normal platelet counts even though the time to achieve the response was variable from a few weeks to several months[5].

A literature review on the role of danazole in adults with refractory ITP has demonstrated that this drug is effective for the disease in lower doses (200 mg-400 mg) with a low dose prednisolone (2.5-5 mg or equivalent) and had fewer hepatic adverse effects. It also suggests that due to the lag effect of danazole, an observational period of 6 months is required to determine its effect. Further studies are warranted to assess long term effects of danazole[6].

A study on rituximab-based combination therapy (oral dexamethasone 40 mg for days 1 to 4, oral cyclosporine 2.5 to 3 mg/kg daily for days 1 to 28, and intravenous low-dose rituximab 100 mg for days 7, 14, 21, and 28) has demonstrated a prolonged response rates in 60% of the study population which included 20 patients with refractory ITP. Severe toxicities had not been reported but low-grade transient side effects related to dexamethasone have been seen[7].

Splenectomy

Previously, failure to respond to splenectomy was included to define refractory ITP. However, at present, there is a need to redefine this disorder without reference to splenectomy due to the general reluctance among both the patients and clinicians towards this option[8]. Therefore, to label as refractory ITP a patient does not necessarily need to have undergone splenectomy.

There are few important factors which can be helpful in considering splenectomy. Studies have shown that younger age (32-51 years versus 40-73 years) and a prior response with IVIg were associated with a response to splenectomy. Nevertheless, another small study has shown that majority (6/7 patients) who failed both IVIg and corticosteroids responded to splenectomy. A high platelet count within the first week after splenectomy has been identified as a predictor of long-term response[9].

Novel and investigational drugs

Avatrombopag is a newer oral TPO-RA which has shown to be safe and well tolerated in refractory ITP. Fostamatinib is a spleen tyrosine kinase inhibitor which has been effective in heavily pretreated patients including TPO-RA, splenectomy and rituximab. Both drugs have been FDA and NICE approved for use in this group of patients.

Novel drugs targeting different mechanisms related to the pathogenesis such as rilzabrutinib (Bruton tyrosine kinase inhibitor), mezagitamab (human IgG1λ monoclonal antibody that binds to CD38) and efgartigimod (human IgG1 antibody Fc-fragment) are some of the drugs which are currently under clinical trials[3].

Other therapeutic strategies

- **Therapeutic plasma exchange (TPE)**

Basturk A et al. based on a multicenter analysis on 17 patients with ITP, have suggested that TPE could be an option for refractory ITP and/ or where immediate platelet rise is required such as bleeding or pre operatively. Nine and seven patients had achieved either complete or partial responses respectively within a mean of 2.5 sessions without serious complications related to the procedure. Removal of the antibodies related to the pathogenesis of the disease has been attributed for its effectiveness[10].

- **Dapsone**

A retrospective analysis which included 58 ITP patients has demonstrated that dapsone is effective in relapsed ITP irrespective of age, sex, ITP types or response to prior treatment. It can be considered when a rapid rise of platelets is not required while the treatment has to be continued for at least 6 months before stopping[11].

AIHA versus refractory AIHA

AIHA is the premature destruction of red cells mediated mainly by autoantibodies or complements but less commonly by macrophages, T lymphocytes or cytokines. It is classified as warm AIHA (wAIHA) or cold type autoimmune haemolytic anaemia (cAIHA) depending on the temperature range in which the auto antibodies show their optimum activity. Occasional patients harbor both warm and cold antibodies and called mixed AIHA[12,13]. WAIHA can be either primary or secondary. CAIHA can be either idiopathic (cold hemagglutinin disease (CHAD)) or secondary to lymphoproliferative disorders or infections[12].

Refractory AIHA is defined in several ways; steroid non response or dependence, failure to respond after 3 treatment modalities, need for treatment after two or more prior treatment lines or dependence on treatment to maintain a response after three or more lines[15].

Rituximab

Rituximab is a chimeric CD20 antibody which induces B cell apoptosis resulting in B cell depletion leading to suppression of B cell mediated production of autoantibodies, cytokine secretion and related functions.

It has been shown to be effective as a single agent or in combination therapy in relapsed /refractory wAIHA or CHAD[16].

A retrospective analysis of use of rituximab in primary or secondary wAIHA, in relapsed /refractory settings, has shown an overall response rate of 70-80% with a median duration of response of 1-2 years while the relapse rate at 1-2 years was 25-50%. A meta-analysis of 21 observational studies on the use of rituximab in adults or children with primary or secondary wAIHA and cAIHA has demonstrated similar results.

In CHAD, use of single agent rituximab or in combination with bendamustine has been associated with good responses and currently recommended in the first line as well as second line settings[16]. Some specialists prefer the former for frail patients and the latter for fit patients[17].

Re-treatment with rituximab for subsequent relapses can be considered if the initial response lasted at least 6 months. Checking for B cell count is indicated as if it is 0, it is unlikely to be effective[18].

Rituximab in combination with intravenous cyclophosphamide and oral or intravenous dexamethasone (RCD) has been shown to be effective in relapsed/ refractory wAIHA associated with chronic lymphocytic leukemia (CLL) as well as without CLL. Infections were reported as adverse effects in immunocompromised patients[16,19].

Plasma cell directed therapy

In refractory AIHA not responding to rituximab, evidence suggests that there is an expansion of long-lived plasma cells lacking CD 20 expression, producing autoreactive antibodies[19]. This understanding has led to the evaluation of plasma cell directed therapies in refractory AIHA.

Bortezomib is a proteosome inhibitor targeting plasma cells which appears to be effective in refractory AIHA according to the limited data available in the literature[14].

Analysis of 6 case reports of adult patients with cAIHA on the use of bortezomib 1.3 mg/m^2 intravenously or subcutaneously from 1 to 13 courses, either as a single agent or in combination with rituximab – dexamethasone or cyclophosphamide – dexamethasone, has shown that all patients have achieved either complete or partial response without significant side effects.

Use of bortezomib in 16 adults with wAIHA either as the single agent or as the combination therapy with rituximab or cyclophosphamide – dexamethasone demonstrated overall response rate of 75%. Adverse effects reported included

thrombocytopenia, neutropenia, peripheral neuropathy and low-grade diarrhea.

Daratumumab is a monoclonal antibody targeting CD 38 antigen on plasma cells. A retrospective analysis on 19 patients with refractory AIHA has suggested that daratumumab monotherapy was an effective and well tolerated treatment option for a proportion of patients with refractory AIHA[20].

Immunosuppressives

Immunosuppressives such as azathioprine, MMF, cyclosporin and cyclophosphamide have been suggested as 3rd and 4th line therapies in wAIHA, refractory or relapsed following steroid therapy[16]. These are found to be less effective in cAIHA[14].

Danazole, as a single therapy or in combination with prednisolone, has been reported to produce responses in wAIHA[6].

Therapeutic plasma exchange (TPE)

TPE removes autoantibodies mediating red cell destruction in the context of AIHA and could be used as a bridging therapy.

In CHAD, TPE is effective in removing IgM antibodies mediating intravascular haemolysis. TPE controls haemolysis temporarily in this context but has no effect on the underlying cause[12].

García-García I et al. reported that in a case series involving 2 patients with wAIHA who had severe haemolysis and were refractory to corticosteroids, IVIg and rituximab initially, improved with addition of TPE every 48 hours for 5-6 TPE sessions. This was combined with low dose IVIg, 200 mg/ kg per every two TPE, weekly rituximab and prednisolone[21].

Erythropoietin

It has been demonstrated that the erythropoietin (EPO) level in patients with AIHA is significantly lower compared to other types of anaemia and endogenous EPO levels are inappropriately low for the degree of anaemia in AIHA[22].

Fattizzo B et al. based on a multicentric study in Europe, have evaluated the safety and efficacy of EPO treatment in AIHA patients. The study population included 51 patients with primary or secondary warm, cold, mixed and direct antiglobulin test (DAT) negative types. A response with a mean Hb increment of >2 g/dL was observed in >70% of patients in both newly diagnosed or relapsed/ refractory chronic disease[22].

Other potential therapeutic agents

A number of agents targeting various lymphocyte antigens have been proposed as potential therapies in refractory AIHA[15]. These include anti CD20 monoclonal antibodies other than rituximab (eg obinutuzumab and ofatumumab), alemtuzumab – an anti CD 52 monoclonal antibody and B-cell receptor inhibitors (ibrutinib and idelalisib).

For wAIHA fostamatinib and several neonatal Fc receptor inhibitors are under investigation.

Despite the availability of multiple therapeutic options, managing refractory cytopenias would still be difficult due to the factors such as individual drug intolerance and side effects, co morbidities, patients' wishes and the local drug unavailability. Therefore, it would be a great challenge for the treating haematologist to maintain safe blood counts amidst all these limitations.

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