Immune thrombocytopenia (ITP) results from a combination of pathological antiplatelet antibodies, impaired megakaryopoiesis and T cell-mediated platelet destruction. Frontline treatment for newly diagnosed (ND) ITP includes prednisone, intravenous immunoglobulin and anti-D (Lambert & Gernsheimer, 2017). High-dose dexamethasone (HDD) is effective in ~85% of adults, but relapse will occur in ~60% (Wei et al, 2016). Low-dose rituximab (100 mg) has been used for ITP, showing an activity similar to 375-mg/m² doses. Sustained response rates of 63–76% have been reported using rituximab plus HDD as frontline therapy (Zaja et al, 2010; Gómez-Almaguer et al, 2013). Eltrombopag stimulates thrombopoiesis, but also suppresses T-cell responses to platelet auto-antigens and induces regulatory T cells (Tregs) (Bao et al, 2010). We have used eltrombopag plus HDD as a feasible first-line therapy, albeit relapses occurred in 30% of patients (Gómez-Almaguer et al, 2014). The lack of sustained responses in adults with ITP has stimulated the search for treatment that could modify the natural course of, and potentially cure, the disease. Thus, we conducted a single centre pilot study to assess the safety and efficacy of triple therapy, including eltrombopag, low-dose rituximab and HDD. This single arm, open-label, study included ND ITP patients from Hospital Universitario ‘Dr. José Eleuterio González’ in Monterrey, Mexico (Clinical trials.gov NCT02834286). Eligible patients were ≥16 years of age, without previous therapy, and ≤30 × 10⁹/L platelets. Bleeding was scored according to the International Working Group (Rodeghiero et al, 2013). Participants were excluded if they had active infection (human immunodeficiency virus, hepatitis), drug-associated thrombocytopenia, malignancy or were pregnant. Our ethics committee approved the study, which was performed in accordance with the Declaration of Helsinki. Outpatient treatment consisted of eltrombopag 50 mg/day for 28 days (1–28), oral dexamethasone 40 mg/day for 4 days (1–4), and low dose rituximab 100 mg weekly for 4 weeks (days 1, 7, 14, and 21). Eltrombopag was suspended if platelets were ≥400 × 10⁹/L. A complete blood count was performed at baseline, on days 3, 5 and 7, and then weekly for 28 days, monthly until month 6, and every 3 months thereafter. Primary outcome was response rate at the end of treatment (day 28). Response and complete response (CR) were defined as an increase in platelet counts ≥30 × 10⁹/L and ≥100 × 10⁹/L, respectively. Secondary outcomes included 2-year relapse-free survival (RFS) considered from the day of initial response until relapse (<30 × 10⁹/L platelets), duration of response (DOR) included the period of time of any responses achieved (CR or response) until relapse. Treatment side effects were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v.4.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). The Kaplan-Meier method was used to calculate probability of RFS; statistical analysis was performed with SPSS software version 20.0 for Mac (IBM, Armonk, NY, USA).

Thirteen consecutive patients were enrolled; their characteristics are reported in Table I. Median follow-up was 14.1 months (range 1.4–24). Median platelet count at diagnosis was 4 × 10⁹/L (range 0–8–28). Median bleeding grade was 2 (range 1–3). All patients responded and all but 1 achieved CR during treatment (92%). Median time to response was 4 days (range 3–10) and to CR 9 days (7–22). Five patients received an additional HDD course due to declining platelet counts; two failed to achieve platelets ≥100 × 10⁹/L at evaluation, thus CR rate at day 28 was 84.6% (response: 100%). Two patients achieved platelets >400 × 10⁹/L (days 14 and 21). One patient was lost to follow-up 2 weeks after response evaluation. One patient lost CR and received danazol for 5 months elsewhere, re-achieving CR and currently remains treatment-free. Two patients relapsed 5 and 12 months after diagnosis; 2-year probability of RFS was 79% (Fig 1). Currently, all but the relapsed patients remain treatment-free in CR.

Median DOR was 11 months (range 0.5–23). Outpatient treatment was well tolerated. One patient reported mild myalgia, 2 had insomnia, and one had fever related to rituximab. Combination short-duration frontline therapy with the rationale of achieving prolonged remissions has not been attempted previously with these three agents. All patients quickly responded and most reached CR, similarly to previous experience with eltrombopag and rituximab plus HDD (Gómez-Almaguer et al, 2013, 2014). The present report can attest to the efficacy of more aggressive therapy early in the course of ITP as it led to an RFS of almost 80% at 12 months that was sustained, in contrast to 66–7% in our previous report with eltrombopag plus HDD (Gómez-Almaguer et al, 2014). Our previous experience with rituximab and HDD showed a similar RFS (84%) at 12 months (Gómez-Almaguer et al, 2013). Interestingly 3 of the 5
patients who received an additional dexamethasone bolus either relapsed or did not achieve a stable CR, therefore better initial responses may predict long-term remission, as previously suggested. (Gómez-Almaguer et al, 2013) Two other studies also have included eltrombopag in ND patients, but not as a frontline therapy; both suggested that the early addition of eltrombopag could be of value before ITP evolves to persistent or chronic phases (Tripathi et al, 2014; González-López et al, 2017). The capacity of eltrombopag and rituximab for improving T cell subsets, particularly Tregs, may help explain these observations (Bao et al, 2010). This strategy could lead to cost-efficiency, with a total cost of US $1400 in our institution, compared with that of continued treatment and loss of work productivity, issues relevant in a limited-resources context (Efficace et al, 2016).

Limitations of our study include a small sample size and lack of a comparative, randomized design. Furthermore, this therapy is not perfect; despite intense treatment some patients lost CR and 2 relapsed, and while the actual long-term DOR remains to be determined, we have achieved an encouraging start, supporting our concept of early, and potentially splenectomy-sparing, management. In summary, we have found that this combination is a safe, highly effective, feasible and relatively durable alternative in ITP. Further investigation is needed to establish if this early ‘total’ therapy approach will enable most patients to achieve long-term CR and treatment-free remission or will only delay relapse and the inevitable onset of chronic ITP.

Acknowledgements

The Universidad Autónoma de Nuevo León funded this study.

Author contributions

DGA designed the research study and wrote the paper. PRCP performed the research study, analysed the data and wrote
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the paper. AGDL analysed the data and wrote the paper. CGA performed the research study and wrote the paper. OGCGR performed the research study and wrote the paper. JCJ designed the research study and wrote the paper.

Conflict of interest

The authors have no competing interests.

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References


We read with interest the recently published article by Milgrom et al (2017) entitled ‘Early-stage Hodgkin lymphoma outcomes after combined modality therapy according to the post-chemotherapy 5-point score: can residual pet-positive disease be cured with radiotherapy alone?’. Their study included 174 patients with early-stage (I-II) Hodgkin lymphoma treated with ABVD (doxorubicin, bleomycin, vincristine; dacarbazine; median 4 cycles, range 2–6) followed by an 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan. Patients were treated with additional radiation therapy (RT) regardless of FDG-PET findings. The prognostic value of post-ABVD FDG-PET results according to the

Post-ABVD biopsy results, and not post-ABVD FDG-PET results, predict outcome in early-stage Hodgkin lymphoma

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Keywords: immune thrombocytopenia, eltrombopag, rituximab, dexamethasone

First published online 21 December 2017
doi: 10.1111/bjh.15070

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British Journal of Haematology, 2019, 184, 279–310