Hypomegakaryocytic thrombocytopenia and increased number of PNH-phenotype cells - an emerging subgroup of myelodysplastic syndrome showing frequent response to immunosuppression - RESPONSE to Rafferty & Leach

Hypomegakaryocytic thrombocytopenia and increased number of PNH-phenotype cells - an emerging subgroup of myelodysplastic syndrome showing frequent response to immunosuppression - RESPONSE to Rafferty & Leach

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RESPONSE to bjh-2017-00124, Rafferty et al.

We read the manuscript by Rafferty et al. with great interest. They described five patients with low-risk myelodysplastic syndrome (MDS) who presented with marked hypomegakaryocytic thrombocytopenia (HMT) and responded well to cyclosporine therapy. All five patients had typical laboratory features of bone marrow (BM) failure with increased paroxysmal nocturnal hemoglobinuria (PNH)-type cells (PNH^+), which included macrocytic anemia, predominant thrombocytopenia, and megakaryocyte hypoplasia(Wang, *et al* 2002). As the authors pointed out, this clinical entity is poorly recognized by clinical hematologists, and therefore, patients with HMT are often treated inappropriately, such as with supportive care alone with transfusions, hypomethylating agents, and allogeneic stem cell transplantation from alternative donors. This is due in part to a recommendation of hypomethylating agents for low-risk MDS patients with thrombocytopenia by the current NCCN guideline (Greenberg, *et al* 2017).

We take a slightly different view from Rafferty et al. regarding the diagnosis of their

patients. They diagnosed their patients with MDS likely based on the presence of erythroid dysplasia and cellular BM. However, dysplastic signs limited to erythroblasts are common in patient with non-severe aplastic anemia (NSAA). The current British guideline for the diagnosis and management of AA describes erythroid dysplasia as a feature of AA(Killick, *et al* 2016). Assessing BM cellularity in patients with BM failure is often difficult, particularly when cytopenia is not severe(Nakao and Gale 2016). Even when the BM of one bone site is grossly replaced with fat tissue, some hematopoietic nests remain in other bone sites and may show hypercellularity due to increased BM activity that compensates for the decreased hematopoiesis. BM aspiration or biopsies of these hot spots can sometimes produce erroneous results. This is particularly true for PNH^+ BM failure patients in whom magnetic resonance imaging of the spinal and iliac BM usually show a few residual hematopoietic nests in a background of fat tissue(Nishimura, *et al* 2014). We would therefore diagnose these patients with NSAA rather than MDS.

The reason we recommend that cases of PNH^+ BM failure be diagnosed as NSAA is to ensure that physicians choose the appropriate therapy for this type of immune-mediated BM failure. Once a patient is diagnosed with MDS, the patient's physician tends to choose supportive care alone or overtreatment with cytotoxic agents or stem cell transplantation, since MDS is defined as an incurable disease due to abnormalities of hematopoietic stem cells with a propensity to develop acute myeloid leukemia. In reality, however, most PNH^+

patients with moderate pancytopenia respond to cyclosporine monotherapy and achieve therapy-free remission, which corresponds to a cure of BM failure. One exception is a subset of PNH^+ patients carrying HLA-*DRB1*15:01*. These *DRB1*15:01*$^+$ patients are likely to become cyclosporine-dependent despite their very high responsiveness to the immunosuppressant (Nakao, *et al* 1994). Physicians must therefore be careful in reducing the dose of cyclosporine when *DRB1*15:01*$^+$ patients achieve remission after cyclosporine therapy.

Lastly, as we discussed in our manuscript, we would like to emphasize that the detection of increased PNH-type cells in BM failure patients can be substituted for measuring plasma thrombopoietin (TPO) levels; virtually all PNH^+ patients have high plasma thrombopoietin (TPO) levels (>320 pg/ml), and even PNH^- patients show a good response to cyclosporine if their TPO levels are high(Seiki, *et al* 2013).

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