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Opinion

Splenectomy in Auto-Immune Hematologic Disorders: To Do or Not to Do

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The spleen, also known as a blood filter, is similar in structure to a large lymph node. It plays a major role in regard to red blood cells (RBCs), by removing senescent cells and serving as a pool of blood. It is also essential for the immune system: phagocytosis, antibody synthesis, removal of opsonized bacteria and antibody-coated RBCs. It is a center of activity for many immunologic reactions and when it is non-functional or absent, it predisposes to many serious, life threatening infections. After a better understanding of many hematological diseases, splenectomy can be considered a second line standard of care, especially for auto-immune disorders: idiopathic thrombocytopenic purpura (ITP), auto-immune hemolytic anemia (AIHA) and thrombotic thrombocytopenic purpura (TTP). Other less frequent indications were to control a painful splenomegaly, to treat a splenic infection (abscess or septic infarcts), to further treat a resistance to chemotherapy because of a massive splenic infiltration, or absolutely to operate a splenic rupture. Many retrospective analysis are reviewing the outcome of the splenectomy, trying to clarify its indications [1,2].

Idiopathic thrombocytopenic purpura is an auto-immune disorder characterized by platelets destruction after being opsonized by antibodies. The destruction occurs by the macrophages in the spleen. Besides, a decrease in the platelets production is also responsible for the thrombocytopenia seen in ITP. The first line treatment of ITP is a corticotherapy leading to complete or partial responses and recovery of platelet counts in 2/3 of the cases, with only 10 to 30% of the patients maintaining a permanent long stay response. Those who recur are candidates for a second line treatment consisting of either the administration of anti-CD20, splenectomy or the thrombopoietin receptor agonists (TPO-RA) with different response rates and efficacy on platelet recovery, as well as different toxicity/side effects profiles. Indeed, splenectomy was found to be the most efficient treatment with the highest potential curative rate in relapsing ITP. Not only does it act on avoiding macrophage induced destruction of the opsonized platelets, but it also acts on stopping the antibody production after stopping all the interactions between the T and B lymphocytes. According to the International consensus report (ICR), it has a *level C* recommendation (based on expert opinion and panel consensus): clinicians must wait for at least 6 months before proceeding with the splenectomy view the possibility of a spontaneous remission. However, it is a *grade 1B* recommendation (strong recommendation, evidence from randomized trials with important limitations) according to the American Society of Hematology (ASH). It offers a short term response rate (RR) of 80% (55% for the Rituximab and 8% for the TPO-RA) and long term RR at 10 years of 65% (versus 20% for the Rituximab at 3 years, not well assessed, but promising results for TPO-RA with 80% long term control rate). Nevertheless, it is still difficult to predict the response to splenectomy and to select patients who may be better candidates for an invasive surgical procedure compared to the 2 other non-invasive treatments. Kojouri et al. analyzed in their retrospective analysis many variables without a statistical significant result to predict the response to splenectomy. Splenectomy is associated with a 0.2% mortality rate and post-operative complications in 12% of the cases (bleeding, thrombotic events and infections) [3-10].

Auto-immune hemolytic anemia is another auto-immune disorder, where the spleen is involved in the destruction of antibody coated RBCs. Corticosteroids are the mainstay treatment with a RR reaching 90% at 3 weeks (hemoglobin level > 10 g/dL). Nonetheless, only 20% of the patients will remain in long term remission after reducing and stopping the steroids. The patients who are refractory to the corticotherapy are subject to receive a second line treatment with Rituximab or splenectomy (other immunosuppressive options also exist). There is no consensus regarding which option is better, as there are no prospective, randomized trials comparing the second-line treatments. Splenectomy has been preferred for many years, but the use of Rituximab as a second-line agent has been gaining favor in the last decade. Splenectomy has been advised as the most effective second-line treatment for warm AIHA after the failure of glucocorticoids, knowing also that its efficacy has never been compared with the other available second-line therapies. It was shown to be nearly as efficient as glucocorticoids in reducing hemolysis and is considered as the only curative regimen. A short-term improvement in the anemia following splenectomy is usually seen within 2 weeks after the surgery in 75% of the patients. Among those who responded to the splenectomy, 20% will be cured without any further medication or immunosuppressive treatment. Yet, among the 50% of those who achieve remission, glucocorticoids in lower doses than

necessary before splenectomy will be required to maintain the remission, and 35% will relapse requiring a third line treatment. At the other side, a targeted treatment with anti CD20 will result in a variable, unpredictable response: 40-100% RR according to the previous trials, and 50% with disease free survival at 2 years; but they cannot be considered cured. In this perspective, Lechner et al., described the splenectomy as the most effective second line treatment for the AIHA with the best short and long terms responses. Nowadays, splenectomy is preferred over Rituximab in the adult population as it is the only modality with a potential for long-term cure, while Rituximab is the treatment of choice for adults who either are not surgical candidates or refuse surgery [11-20].

So far, splenectomy used to be much more recommended for the discussed auto-immune hematological diseases (ITP and AIHA) compared with the thrombotic thrombocytopenic purpura. TTP is a fatal medical emergency necessitating an urgent treatment and plasma exchange initiation. Corticosteroids and Rituximab are the standard of care in TTP. The data supporting splenectomy as a treatment of TTP are limited to case series with no control groups; splenectomy was suggested to be an option for patients with refractory or relapsing diseases. It may be justified by the fact that the spleen is responsible for the destruction of ADAMTS13-antibody complexes and for the production of anti-ADAMTS13 antibodies. To assess the benefit of performing a splenectomy in patients diagnosed with TTP, Dubois et al. reviewed the literature and evaluated the indication and safety of splenectomy for refractory or relapsing TTP. 74 patients who underwent splenectomy for a refractory TTP, were followed for a median period of 39 months, as well as 87 patients who were operated for a relapsing TTP, had a follow up for 53 months. The risk of disease recurrence was less in the group of patients for whom the splenectomy was done for a refractory disease compared to a relapsing TTP (8% vs 17%). Additionally, many case series and reviews reported splenectomy as a successful treatment, though its indication remains controversial nowadays. It lost progressively its place as an early treatment after the advance in plasma exchange techniques, especially that it is associated with a high mortality rate. On the other hand, it was demonstrated to act in relapsing or refractory disease. When TTP recurs, it is usually treated as the first episode, with prompt initiation of plasma exchange, high dose corticosteroids and rituximab. Once these therapies induce remission, it has been shown that a preventive care might be beneficial: administration of rituximab upon decrease in ADAMTS13 activity, maintenance rituximab independent of ADAMTS13 activity, other immunosuppressive therapies or splenectomy aiming to clear the clones of lymphocytes responsible for ADAMTS13 antibodies. Data on preventive splenectomy are of expert opinion as it is mainly recommended after a remission following frequent relapse. The rationale behind the splenectomy in treating refractory relapsing TTP is the eradication of ADAMTS13-specific memory B cells. This was demonstrated by Schaller et al. after putting splenic cells from refractory acquired TTP in culture; surprisingly, the cultured cells were able to produce anti-ADAMTS13 immunoglobulin G antibodies that shared common complementarity-determining regions. Thus, the two patients from whom splenic cultures were done underwent splenectomy and have been free of relapse with normal ADAMTS13 activity for 8 and 11 years. Despite these encouraging results, splenectomy is not a standard of care in TTP, where plasma exchange therapy, corticosteroids and rituximab showed very good results. However, knowing that clonal B cell residing in the spleen may be responsible for a resistant, refractory relapsing disease, splenectomy can be considered an option after balancing the risks-benefits of the procedure [21-29].

Consequently, the spleen is an important lymphoid organ playing a major role in the immune-regulation and serving as the field of the cellular destruction in the auto-immune diseases. With its imminent involvement in immune reactions as a pool of B and T lymphocytes, and the current knowledge of its purpose in the removal of old red blood cells and platelets, splenectomy has been a rescue treatment after failure of the standard therapies. Patients should be evaluated and properly selected after balancing the short and long term risks against the potential benefits knowing the disease biology: risks related to the surgical procedure itself and much more, those related to the underlying splenectomy indication.

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