Interview

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International Journal of Hematologic Oncology

The importance of early intervention in the treatment of hepatic veno-occlusive disease

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Antonio Pagliuca is Professor of hematopoietic stem cell transplantation at King's College London (UK) and medical director at King's College Hospital where, until last year, he had been the transplant director for the past 24 years. He also has roles within NHS England as national clinical lead for regenerative medicine and is a trustee on both the Anthony Nolan trust (London, UK) and Leukemia UK (London, UK).

Here he speaks to Commissioning Editor Jennifer Straiton and discusses the interim results of the DEFIFrance study, recently presented at the European Society for Blood and Marrow Transplant (EBMT), which looked at the real-world use of the European Society for Blood and Marrow Transplant severity grading criteria. The study investigates the use of defibrotide as a treatment of patients with post-transplant hepatic veno-occlusive disease and demonstrates how it can benefit from early intervention.

First draft submitted: 24 April 2019; Accepted for publication: 24 April 2019; Published online: 11 July 2019

Keywords: defibrotide • stem cell transplant • veno-occlusive disease

Could you give a short background to hepatic veno-occlusive disease; what causes it & what are the present treatment options?

Typically, hepatic veno-occlusive disease (VOD) is a disorder seen following bone marrow transplantation, with some of the first descriptions of the disease being made within the transplant community in the 1970s and 1980s. We soon became aware that VOD is related to certain treatments that patients were receiving, the alkylating agents and other drugs being used were found to cause an irritation of the endothelium within the hepatic vessels. This led to inflammation and microthromboses of the liver parenchyma, with patients presenting with three classical features: they would start to gain weight, have right upper quadrant tenderness and see a rise in their bilirubin, making them appear yellow. After the appearance of these symptoms, some patients would develop kidney failure. Though only affecting a small proportion of patients, it can be an absolutely devastating side effect.

Over time, we have gained a better understanding of how the problem arises, which has enabled us to modify the way we treat it and has reduced incidence. In historical data, the incidence was shown to be about 14%, though with improvements in reduced toxicity transplants, I have seen this reduce to around 6%.

With regard to treatment options, most of us primarily use ursodiol (ursodeoxycholic acid) as a prophylactic agent for preventing the development of hepatic VOD. However, we still have to anticipate and see what happens with these patients and then, if we believe the patient has satisfied the diagnostic criteria, we get them started on defibrotide, the only licensed agent for the management of VOD. Right now, the most commonly used criteria for determining the development of VOD would be the Baltimore criteria, which takes into account the parameters of the three key symptoms.

What makes early treatment & intervention so important in VOD?

What the recent DEFIFrance study has done is demonstrate the important of early treatment, intervening before the disease gets to the very severe stage. By using the new EBMT severity criteria to separate patients into severe and very severe VOD categories, it allowed us to see that the outcome of the patients in the very severe category is significantly worse that the patients in the severe category.

In the study, the severe VOD population had a survival rate at 100 days of 85%, in the very severe group this reduced to as low as 32%; that is a lot of patients who are succumbing or dying from the toxicities of VOD that, at

earlier intervention, could have improved. This study really showed that it is better to start treatment early, before the disease can progress, and in as rapid a speed as possible.

What clinical impact do you think the results of this study will have?

The whole purpose of having a stem cell transplant is not to develop VOD, it is to cure the underlying disease, typically leukemia or lymphoma. These are already difficult enough diseases to cure and so really, the worst thing is that the patients do not die due to relapse, but they die of one of these consequences of treatment. If we can overcome this transplant-related mortality by treating patients promptly and intervening earlier then the patient will hopefully survive long term having got through VOD and, hopefully, also having cured their underlying leukemia or lymphoma. As the results of the study show, starting this practice in the clinic could potentially reduce VOD mortality by 50%.

What further advances do you envisage with respect to treatment of VOD in the coming years?

I think there are lots of things happening in this space. There has been a lot of discussion about having better diagnostic methods and biomarker tests. At the recent EBMT meeting, there were some data presented on a very simple score called the EASIX score which looks at three very simple parameters, LDH, creatinine and platelets, which should allow us to define and diagnose these patients much earlier. Together with the EBMT severity criteria, this will hopefully provide better assurance that these patients actually have VOD rather than one of the other disorders that can mimic VOD symptoms. While early diagnosis is important, we also need to make sure it is correct, so I think the diagnostics and biomarkers are going to be very helpful in that situation.

The consensus in most disorders is that it is better to give a prophylactic rather than therapeutic treatment, like having a vaccination. There is an on-going study to see if we can use defibrotide as a prophylactic for patients who are considered high risk of developing VOD which, if the data pans out, should help in reducing the incidence of patients with the disorder.

This is difficult group of patients and can be a hard disorder to treat so I think that it is a really important area for us to improve in and develop further options for.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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