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Newsletter

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A Transplant Physician's Journey

Over the last three decades, Joanne Kurtzberg, MD., has established a leading Pediatric Blood and Marrow Transplant Program at Duke University Medical Center in the United States which treats children with cancer, blood disorders, immune deficiencies, hemoglobinopathies and inherited metabolic diseases.

Dr Kurtzberg is the senior investigator in Mesoblast's completed Phase 3 trial in 55 children with steroid-refractory acute graft versus host disease (aGVHD) and in the previous Expanded Access Program (EAP) in 241 children.

Dr Kurtzberg recently spoke about her experiences as a transplant physician and her experiences treating children with aGVHD.

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What causes graft versus host disease after an allogeneic (unrelated donor) bone marrow transplant?

Graft versus host disease is the most serious complication of an allogeneic transplant and it occurs when the donor cells that have engrafted in the patient attack the patient's organs. There are various forms of graft versus host disease. The mildest form involves skin only and causes rashes of various types but the more severe forms involve the intestines and the liver and sometimes other organs as well, and are life-threatening.

How common is GVHD?

The incidence depends a little bit on the type of transplant the child has or type of donor that is used. But up to 50% of children who have an allogeneic transplant can develop graft versus host disease.

What's the prognosis for these children?

So the prognosis is also varied. Children who have just skin involvement have a good prognosis and that generally responds to steroids or other common therapies. But children who have visceral organ involvement, meaning intestinal involvement or liver involvement, have a dismal prognosis where 70% to 90% of children will die.

What's the current treatment algorithm?

The usual treatment algorithm is to use steroids systemically - if the child has systemic symptoms; so either very profound rash all over their body or diarrhoea, vomiting, liver dysfunction, fevers or blood dyscrasias (blood abnormalities). Steroids are the first line of therapy. They're generally given intravenously and within a few days you can really tell if a patient is going to respond or not.

If children under 12 do not respond to steroids, there is no proven effective therapy beyond that point but there are multiple different drugs, all of which are immunosuppressive and also have other toxicities, that are tried. Generally different centers have a different order in which they use these drugs but over the course of two or three weeks, the child could be exposed to five or six more agents.

What happens if these multiple agents don't work?

If these multiple agents don't work, generally over the next several months the child dies.

Also, these multiple agents cause other problems lowering immune systems, so many children with active GHVD die of an infection because they can't fight off any infections without a functioning immune system.

Given that GVHD is such a serious and potentially life-threatening condition, as someone who has been practising for a long time with children and dealing with families on a day to day basis with this devastating disease, how do you cope?

Gosh, that's a hard question. The most important thing that a pediatric transplanter has to do is medically care for a child but equally importantly you have to support that child's parents and family through the process.

I don't do anything special to cope, but I do make sure that in addition to caring for these kids, my team and myself are participating in research that can improve the outcome of the complications of the process.

So I'm inspired, I guess, and motivated by participating in research that I know can make a difference while I care for these children… because GVHD is such a challenge.

If you can picture it, you have a child who has a life-threatening disorder. You do the transplant and it's successful, meaning it engrafts. So there is tremendous hope that that child will be okay, and then a week or months later, they get this devastating, again life-threatening, disease that may sabotage the success of the original procedure. So it's traumatic, it's scary. It produces a lot of discomfort in the child because of the symptoms but also just worry in the medical team and in the parents that a child who looked like they'll make it but won't. So it's a very high anxiety situation.

Where could remestemcel-L fit into this treatment algorithm?

Remestemcel-L initially was tested on an expanded access protocol in 241 children who had steroid-refractory GVHD and also in general had received other agents and failed. It was given to these children over a one to two month treatment course and was shown to have a very significant effect in calming down the GVHD in nearly 70% or so of those children, and of the children who responded, their survival was dramatically improved at six months post treatment.

After that, because of those very encouraging results and because of the need to bring it to the clinic and get FDA approval, an open-label Phase 3 study was conducted in 55 children testing remestemcel-L as a first line agent after a child failed steroids. So on this Phase 3 trial, children would be given steroids and if they didn't respond within three to seven days, they were eligible to receive remestemcel-L and they couldn't receive other agents while they were treated with remestemcel-L.

On that trial, essentially the observations of the first study were replicated – 69% of the children achieved complete response or partial response at 28 days and again that greatly improved survival both at 100 days and six months post treatment.

As a pediatric transplanter who cares for children with graft versus host disease, it's one of the most promising agents that I've seen in my entire career targeted for children with steroid-refractory GVHD.

In addition, in the children I have treated with remestemcel-L, it was very well tolerated, it didn't have any appreciable side effects and it didn't appear to cross-react with other drugs that these children have to take as supportive care after their transplant.

I also didn't see any evidence that it attacked the kidneys or affected the kidneys, or significantly suppressed the immune system.

So, in my experience, it was well tolerated without overlapping side effects and helped improve the GVHD of these kids.

Mesoblast recently initiated the rolling Biologics License Application to the FDA. What's your reaction to this news?

It makes me feel good. I'm really happy that Mesoblast submitted the first module of their BLA.

I hope that this results in approval.

Based on my experience with children refractory to steroid treatment, if approved, remestemcel-L could meet a critical need for children under 12, given that there is no other approved therapy today available for this group of patients.

The views, thoughts, and opinions expressed in the interview above are solely those of Dr Kurtzberg expressed freely in an interview for which she was not compensated. These views are not necessarily shared by Dr Kurtzberg's employer, institution, or any other group or individual. Results described may vary among patients.

Following the recent initiation of the rolling Biologics License Application (BLA) with the United States Food and Drug Administration (FDA), Mesoblast expects to complete its submission for remestemcel-L in children with steroid-refractory acute graft versus host disease (aGVHD) in the second half of 2019.