Emmes

Challenges of conducting clinical trials in rare hematologic disorders:

A focus on hematopoietic cell transplantation

Introduction

Researching novel treatment options for patients with rare blood and marrow disorder is incredibly complex because of the limited numbers of patients, heterogenous group of disorders, variety of treatment modalities, and the need for specialized physicians. One major class of treatments that is considered the standard of care is the use of blood or marrow cells from a related or unrelated donor known as a hematopoietic cell transplant, commonly referred to as HCT.

This procedure infuses healthy blood-forming (hematopoietic) stem cells from a healthy person's bone marrow into a person with a blood disorder to replace their abnormal stem cells. Bone marrow is a source of hematopoietic stem cells includingred and white blood cells and platelets. This life saving intervention has been undergoing research since 1956 when the first successful bone marrow transplant was performed by Dr. E. Donnall Thomas.[1]

Since then, it is estimated that over one million HCT have been performed globally. However, this doesn't come without significant risk of morbidity and mortality. As the technology and treatment options are better understood and tested in various malignant and non-malignant disorders, more question are raised regarding the optimization of therapy for these patients. Since 1995, Emmes has been at the forefront of HCT research and have been involved in major practice changing studies.

More recently, with the advances in gene editing and modification, Emmes is working on novel treatments for patients with various disorders including sickle cell disease and multiple myeloma. Following is a perspective on what Emmes has learned over two and a half decades in researching rare hematologic disorders.

Impact of HCT on Patients and Families

HCT has the potential for a cure of the underlying disease. However, the process is complex and also has a risk of death[2,3,4]. There are long stays at hospitals that specialize in HCT that may not be located near home. In addition, the donated stem cells might not engraft; i.e., the therapy doesn't work as hoped because the healthy donor's cells do not start to grow and make healthy blood cells in the patient. Other known serious treatment-complications include infections and graft vs. host disease (GvHD), a disease in which the donated stem cells view the patient's body as foreign, and attack the body's skin, liver or gastrointestinal tract.

Furthermore, the underlying cancer may return which is known as relapse. Improved ways to administer HCT as well as improved ways to prevent or manage known HCT complications, are both desperately needed. Here at Emmes we have a long history of supporting HCT research and managing key breakthroughs in the field.

We have supported some of the earliest large studies into unrelated donor transplants[5,6,7] and optimizing transplantation including using stem cells from not only bone marrow, but also peripheral (i.e. blood circulating around the body)5 and umbilical cord blood[8].

In addition, Emmes is supporting trials for two other rare diseases, aplastic anemia and sickle cell anemia, using haploidentical transplant in which a family member whose tissue type is half-matched to the patient is used as the donor for patients[9,10].

We continue to expand the use of HCT into broader populations such as older patients[11] and we are exploring new indications such as gene therapy for sickle cell disease and chimeric antigen receptor (CAR) Tcells[1] to improve post HCT responses among patients with multiple myeloma (MM)[12]. We're also using this knowledge to support research into improvements needed to prevent or mitigate known HCT- complications that can have very serious consequences for patients[13–17].

Throughout this time, we have formed many long-term and fruitful partnerships with centers of excellence such as the Center for International Blood and Marrow Transplant Research (CIBMTR)[17] and the National Marrow Donor Program (NMDP)/Be the Match®, the world's largest and most diverse donor registry containing nearly 12.5 million potential marrow or blood donors and more than 209,000 donated cord blood units[18].

Alongside these leaders, we continue to develop a rich understanding of unmet needs, we have enhanced our capabilities, and we continue to deliver our trials with efficiency and care.

During our series of white papers, we have shared insights into optimized trial delivery, patient population requirements, trial design, and biostatistics are highly relevant and have been discussed previously. HCT trials are a specialty of their own due to the demands of the hematological condition and unique treatments being used. We'd like to continue our series by sharing some key aspects to consider before embarking on research both as a participant and for those involved in trial design/delivery.

[1] CAR T is a process where some of the patient's own T-cells are removed from their blood and have small changes made. These modifiied cells are then given back to the patient (via an intravenous drip) and can now identify and attack the patient's cancer

Site selection and recruitment

Emmes has developed over 140 working partnerships with clinical centers who specialize in treating patients with HCT. Each institution has unique therapeutic strengths and research focuses. Some centers specialize in umbilical cord transplants and others, haploidentical transplants (i.e. from a matched donor such as a family member).

In addition, some centers are disease-focused, being the leading hospitals in conditions such as sickle cell disease or multiple myeloma. Knowing this information ensures that we can align with each center's areas of interest and boost recruitment to the study through optimized site selection in our trials.

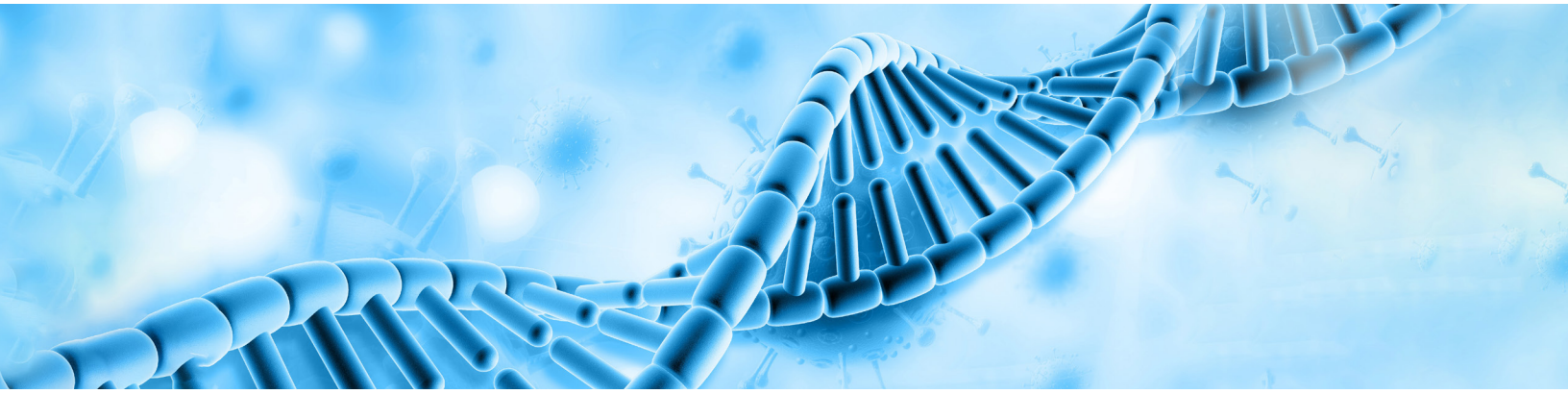
Patients referred for HCT have often failed prior therapies and thus have a shortened life expectancy. Decisions need to be made, and therapies need to start quickly. Patients can only be presented with the possibility of a trial by their physician after decisions have been made about which treatment options are suitable for them.

Therefore, rapid agreement as to whether HCT is a treatment option, followed by smooth coordination between hematologists/oncologists and transplant physicians is beneficial for all.

Support materials for patients and their families also need to be developed in a way that accessible and understanding of the situation they are in at the time of taking decisions. Because of the nature of the disease and the complexity of the treatment, undertaking HCT is a full-time commitment for not only the patients but also their families and support groups. This may limit much needed fast recruitment.

There is clearly a need for culturally sensitive, realistic, and lay friendly communication to further enhance people's willingness to take part in this type of clinical research. An example of this is gene therapy, where little is usually known by patients before the treatment option is suggested to patients and families by their treating physician.

There is a need to ensure that patient/caregiver-centered education about gene therapy isprovided, and then supported by ongoing and innovative strategies to engage patients as research "partners" instead of research "subjects". One such model for engagement that has been used for patients with sickle cell disease is Community Health Ambassadors that serve as liaisons to engage patients in projects such as patient-centered outcomes research.[2]



Picking active sites

One way of accounting for challenging recruitment situations is to try and involve more sites and countries in a trial. While this is may be essential for many rare diseases, and can be a useful strategy, site selection should always be driven by robust information. Data from national registries such as the CIDMTR[20] and the European Bone Marrow Transplant Registry[21] provides an unbiased insight into which centers most actively treat patients with di erent types of HCT.

Aligning priorities

Aligning the trial's primary research question with the site's specialist research focus supports rapidrecruitment for a trial. If not done, an excellent center may be able to deliver a trial that focuses on, for example, treatment using stem cells from matched volunteers (usually family) but is unlikely to be optimized for recruiting a trial using cells from umbilical cords.

Understanding competing priorities

Another optimization technique is to asses the list of other trials the centers have ongoing at the same time. These trials are likely to also be trying to recruit the same patients and this alters the number that might choose yours. Recruitment expectations should be amended accordingly to ensure the are realistic.

Being heard

Not all specialists treating patients within a center will be directly involved in the trial-team. If information about the trial can be shared amongst sta , the number of specialists who refer patients to the trial team increases. We have observed that having study champions within sites advocating for the study is a larger predicator of recruitment success.

Figure 1: considerations for site selection and enhancing trial recruitment Employing these approaches Emmes has establisheda long history of recruiting to complex trials and providing the interventions required to turn around struggling trials and exceed recruitment expectations.

Flexible eligibility criteria

Eligibility criteria are the rules put in place to ensure that the people offered the trial are likely to be those most suitable for receiving the experimental medicine. The way in which diseases requiring HCT intervention affects people can vary dramatically. This changes the risk of therapy – both for themselves and for the integrity of the study.

For the study to produce useful results that are robust and can change care in the future, criteria used for trial population-selection need to be developed and fully informed by clinical study specialists.

Broadening eligibility criteria is difficult for HCT interventions because of the many nuances and specificities that need to be preserved. However, where possible, changes can benefit both patients and researchers by ensuring that as many as possible can access investigational drugs.

Over the years at Emmes we have worked with the specialty centers to acknowledge the realities of these conditions and gather data to change the ‘eligibility criteria’ for trials.

This means that we are in a position to have an informed discussion with sponsor companies about their trials; ensuring that each eligibility criterion is appropriate for that patient group, the sites delivering the studies, and the known risks of the treatment being developed. This informed collaboration maximizes the chance that the trial will be offered to a broad population, in a way that continues to keep them as safe as possible.

Trial monitoring

The complexity of HCT treatments, variation in standard care approaches regionally and globally, and the number of serious complications that can occur during therapy, make these trials extremely demanding for those taking part.

Clinical monitoring of these patients is also more involved and requires a high level of training. A deep understanding of the condition being treated is essential, along with the specifics of treatment delivery, and the ability to spot early warning signs when complications occur in this complex setting. In addition to this, staff need to balance the standard of care procedures to undertake for their patients as well as the requirements of a research protocol.

Clinical research organization (CRO) staff support patients and clinical centers throughout, by monitoring safety data coming from all sites to try to spot patterns and signals that can only be detected in the larger, aggregated data sets. As HCT comes with an underlying risk of significant morbidity and mortality, Emmes additionally deploys statistical methods. These build in what we know about underlying risks and use a sequential probability ratio test to monitor fundamental safety outcomes such as early death, graft failure, and toxicity.

One of the places that Emmes is known as a leader in transplant and gene-therapy is the approach to data collection, including how safety data is managed. These are complex patients where the data reporting system could be overwhelmed by the amount of conmeds, infections, GVHD and AEs, but our approach to streamline this collection meets the needs of our clients – both government and biopharma.

Statistical Analyses

Informed analytical approaches must also be used at the end of the trial. The studies are designed to differentiate treatment-related effects from all the other health concerns and competing risks that are routine for HCT. This often requires specialized methods and modeling that have been designed into the trial from the start. Even for studies where the treatment ultimately fails to improve a patient's condition, it's important to see through the myriad of medications and comorbidities the patients present with and understand ***'why?'.***

With advances in statistical computation, it is possible to assess directly the benefit of treatment on a primary cause of failure in a clinical trial setting. Then statistical modeling is used to adjust for residual imbalances in patient characteristics, improving the power to detect treatment differences. Answering the key questions even in the worst-case scenario[22].

Conclusion

Technology is advancing rapidly in the fields of gene and cellular therapy. The refined processing of these cells means that genetic manipulation can be undertaken, and the number and range of conditions that this life-saving therapeutic approach can be used for is increasing.

As with other ground-breaking steps, Emmes continues to be on the front face of these advances, recently expanding the number of trials using cell and gene therapy for nonmalignant disorders.

It is only through intensive monitoring of safety, advanced analytical methods to detect warning signs earlier, and the novel ways that treatment results can be evaluated, that will push the fields of research further whilst also placing patient safety and quality of life first.

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