INFECTIOUS DISEASES IN THE IMMUNOCOMPROMISED HOST

A DYNAMIC LANDSCAPE WITH CHALLENGES FOR CLINICAL DEVELOPMENT

Changes in antitumor therapy and hematopoietic cell transplantation (HCT, or bone marrow transplantation) are affecting the pattern of immunosuppression previously known in immunocompromised patients. The shift from myeloablative treatment of leukemia, as well as conditioning regimen for HCT, to a more targeted or immunomodulatory approach, combined with the increasing indications and number of unconventional graft sources, are affecting a shift from depletion of the innate immune system (intense neutropenia followed by relative lymphopenia recovering within a few months) to a depletion of the specific immune system (targeting B or T cell depending on the regimen) for longer periods of time.

These changes in hematology-oncology therapeutics are leading to changes in nature (e.g., from bacterial to viral), pathophysiology (e.g., reactivation versus or combined with primary infection), the incidence of, and therapeutic approach for infections in immunocompromised patients. Furthermore, the timing of these infections are starting to shift from those defined during the myeloablative era. Following a worldwide increase in resistant bacteria, the emergence of multi-drug resistant strains has also affected hematological wards, including the HCT setting. The clinical impact of resistant bacteria is worrisome, with increasing mortality of infections produced by these strains.

Important considerations for conducting infectious disease clinical trials in immunocompromised hosts:

- Therapeutic approaches for hematologic malignancies
- Changes in the incidence, nature, epidemiology, timing, and resistance profiles
- Identification of the growing current unmet medical needs for immunocompromised patients
- Challenges in the design and implementation of development programs

THERAPEUTIC APPROACHES IN CELL AND GENE THERAPY FOR HEMATOLOGIC MALIGNANCIES

Cell and gene therapies have led to multiple FDA-approved products in the United States and elsewhere. The most well-described of these are those products with chimeric antigen receptor T-lymphocytes. Amongst products currently approved by the Food and Drug Administration are tisagenlecleucel for B-cell precursor acute lymphoblastic leukemia, and axicabtagene for adults with diffuse large B-cell lymphoma. Further, there are quite a few more products in clinical development.

The current FDA-approved products are manufactured from autologous T-lymphocytes obtained from patients. They are subsequently transduced with a gene product, leading to the installation of a chimeric antigen receptor specific for an antigen expressed on the malignancy. They are typically administered following a chemotherapy regimen designed to lymphodeplete the patient. Adverse events associated with the administration of these products can be serious infections, largely due to the chemotherapy administered in combination with these products. There does tend to be a period of protracted neutropenia, approximately four to six weeks, and, depending on the target, one can develop hypogammaglobulinemia.

The FDA-approved products currently on the market are directed against the CD19 B-cell, leading to hypogammaglobulinemia due to protracted B-cell depletion. Other gene-modified products are in development and can be considered for single-gene diseases. These may either involve using committed cells to fight viral infections or using hematopoietic progenitor cells to correct hereditary disorders. In any case, many of these agents do require administration of chemotherapy, either for myeloablation or lymphoablation, to allow selective expansion of the transduced cells.

BLINATUMOMAB DEVELOPMENTS

Blinatumomab is part of the bispecific T-cell engager class of medications or BiTE antibodies. These are constructs designed to bridge CD3-positive cytotoxic T-lymphocytes to cells expressing a specific cell surface antigen, in this case, CD19. This leads to the release of proteolytic agents, which can then destroy the malignant cell. Infections are observed in a significant number of patients in the early studies, estimated to be up to 25 percent, largely due to neutropenia.

Infectious complications with blinatumomab as a single agent are typically less than that observed with multiagent chemotherapy. However, blinatumomab is currently used as a second-line therapy in patients with relapsed, refractory or MRD-positive acute lymphoblastic leukemia, and these patients are already immunocompromised from their extensive prior therapies.

ANITBODY DRUG CONJUGATES

Building on the antibody regimens, antibody drug conjugate links an antibody with a toxin designed for specific delivery to a cell expressing a specific antigen. The toxin is then internalized by the cell, leading to the death of that cell.

Antibody drug conjugates:

- Gemtuzumab ozogamicin - directed against CD33, which is expressed on malignant and nonmalignant myeloid cell
- Inotuzumab ozogamicin - targets CD22 malignant and nonmalignant B-lymphocytes, leading to B-cell lymphopenia as well as neutropenia
- Brentuximab vedotin - directed against CD30 and expressed on Reed Sternberg cells as well as activated T-cells

CHECKPOINT INHIBITORS

Checkpoint inhibitors are agents that regulate T-cell activity during the body's immune response. These checkpoint inhibitors are designed to enhance T-cell activity against malignant clones and include such targets as CTLA-4, PD-1, and PD-L1. These agents have the lowest risk of infectious complications of the agents discussed. The most important factor to recognize is that these agents are more likely to lead to autoimmune organ toxicity, such as pneumonitis, hepatitis and colitis. However, infectious etiologies in these patients must be excluded. Treatment for these autoimmune responses do require discontinuation of the agent in many cases and administration of steroids, thus increasing the infection risk.

CHANGES IN INCIDENCE, NATURE, EPIDEMIOLOGY, TIMING, AND RESISTANCE PROFILES

A review of a multicenter, prospective and cohort study showing information on the epidemiology and timing of infection in four important U.S. HCT centers provides a picture of the current landscape in this field. In the study, 444 HCT recipients showed the following results after 30 months:

- Bacteremia occured in 231 (52%) cases and ocurred early post-transplant (median day 48)
- Gram-negative bacteremia infections were less frequent than Gram-positive, but it was associated with higher mortality (45% vs 13%, P = .02)
- Clostridium difficile: 148 patients (33%). Median of 27 days post-HCT

A few key findings to note are the high rates of bacteremia in the period post-transplant and the high mortality in gram-negative infection. The high rate of antimicrobial resistance in those sites is probably the main cause of these bad outcomes. Another important point recognized recently with a growing prevalence is clostridium difficile. This is an important problem in this population that usually appears in the first months after transplant. The recurrence rate of this infection is also very high.

About 10 percent of the patients in the study presented fungal invasive infections. Around 10 to 15 years ago, most of these infections were identified before the engraftment. Now, there is a shift in the timing and most of these cases were late infections. Approximately 35 percent of the patients experienced an episode of cytomegalovirus (CMV) infection, but only 4 percent developed disease organ involvement. This very low compromise of organs is directly related to the implementation of effective antiviral strategies on this population.

The rising problem with CMV is the development of antiviral resistance to Valganciclovir. Some approaches for CMV prevention like vaccines and adoptive immunotherapy are under development. Respiratory viruses are also a common problem. Around 10 percent of this population is affected by other viruses such as respiratory syncytial viruses (RSV), influenza, and adenovirus, for which therapeutic alternatives are limited and toxic right now.

EPIDEMIOLOGY PATTERNS OF SELECTED INFECTIONS IN IMMUNOCOMPROMISED HOSTS

Epidemiological issues with bacterial, fungal and viral infections in this population include:

Bacterial infections: Treating infections, most commonly gram-negative bacteremia, is one of the main unresolved problems in this population. There is an unmet need for new drugs to treat multidrug-resistant bacterial infections. The percentage of bacterial resistance and mortality rates are very high. The main challenge lies in choosing an effective empirical antibacterial regimen since standard options might prove inadequate. Alterations of the microbiome in patients receiving broad-spectrum antibiotics have been implicated in the genesis or severity of acute graft versus host disease.

Fungal infections: Fungal infections are an important complication in patients with cancer and recipients of stem cell transplants. Multiple factors including exposures, antifungal prophylaxis, iron overload, concomitant infections, underlying hematological disease, and continuous immunosuppression have influence in the emergence of resistant fungal strains. However, the timing of these fungal infections has changed. Fungal infections are identified as late infectious complications due to prolonged survival of patients and successful prophylaxis strategies. Further, fungal species including, azoles resistance, aspergillus, zygomycetes, fusarium, are more difficult to efficiently treat with a limited number of antifungal agents available.

Viral infections: The herpes virus genus is known to lead to latent infections that develop in immunocompetent hosts, and then would reactivate as a result of the immunosuppression. Respiratory viruses are also more easily identified, especially as a result of improvement in the assays available and with more availability of therapies. Both herpes reactivation and respiratory viruses are primary infections in most cases (although adenovirus can be recurrent) and are mainly a result of T-cell depletion. B-cell depletion is mostly known as inducing progressive multifocal leukoencephalopathy (PML) as a result of JC viruses, and broadly, result in polyomaviruses reactivation with nephropathy or cystitis associated with BK virus.

CHALLENGES IN CLINICAL DEVELOPMENT

There are several challenges to consider when trying to develop drugs to mitigate infections in the immunocompromised patient population. These are rare and life-threatening infections in a population that is complex. Usually, there is no approved drug and certainly, we're limited in development programs. Planning for study design challenges, implementation challenges, and data considerations are critical for successful clinical trials in the immunocompromised patient population.

Study Design Challenges

- **Early interaction and education of regulatory agencies:** Interacting early with regulatory agencies is paramount. Educating them about the importance of the unmet medical need, the specificity of the morbidity and the mortality of those infections, their importance, and what the current standard of care is important in ensuring success in negotiations.
- **Choice of comparator drug:** Very few drugs are approved for use in the immunocompromised patient population. Moreover, developing a new antibiotic can be difficult in patients when an agency is more likely to push drugs that are already approved.
- **Clinical versus surrogate endpoint:** From a design standpoint, the endpoint can be a difficult discussion with agencies where it may be more appropriate to rely on a surrogate endpoint versus a clinical endpoint. Agencies generally want a more clinical type of endpoint, which may or may not always be feasible. Natural history studies are helpful in defining the correlation between surrogate and clinical endpoints.
- **Drug interaction considerations:** The average concomitant drugs in a bone marrow transplant patient are 25 to 30. Sponsors need to have a clear plan for drug interaction measurements and management during a clinical trial.
- **Prevention, preemption or therapeutic approach based on incidence and safety profile:** Choosing the timing of intervention is important. The therapeutic approach would probably require a small number of patients. However, it may be more limited in its impact, because the end-organ disease may or may not be reversible. When the nervous system is destroyed by the infection, stopping a viral infection is probably not going to make the patient recover, but preventions and prevention approaches for relatively rare infections may require a much larger clinical trial. In addition, the safety profile of the compound would probably dictate what phase is the most appropriate with prevention requiring a very well-tolerated regimen as patients would receive the drug mostly while they may not develop the infection.
- **Frequency of co-infection:** Data shows that co-infection by multiple viruses is theoretically common and this will need to be addressed in the design. If the drug has activity against multiple viruses, one wants to make sure that the dosing of the drug will not create resistance against one while trying to prevent or treat another one.
- **Balance population homogeneity versus generalizability of findings:** Finding the adequate patient population is a balance between trying to homogenize the patient population and having a result that can be generalized to a broader patient population. That is a balance between recruitment on one hand and interpretation of the results on the other.
- **Immunity guided duration of therapy:** Duration of therapy for the proposed regimens is a complex definition and research regarding the degree of immunity, reconstitution that could guide the duration of therapy is warranted.

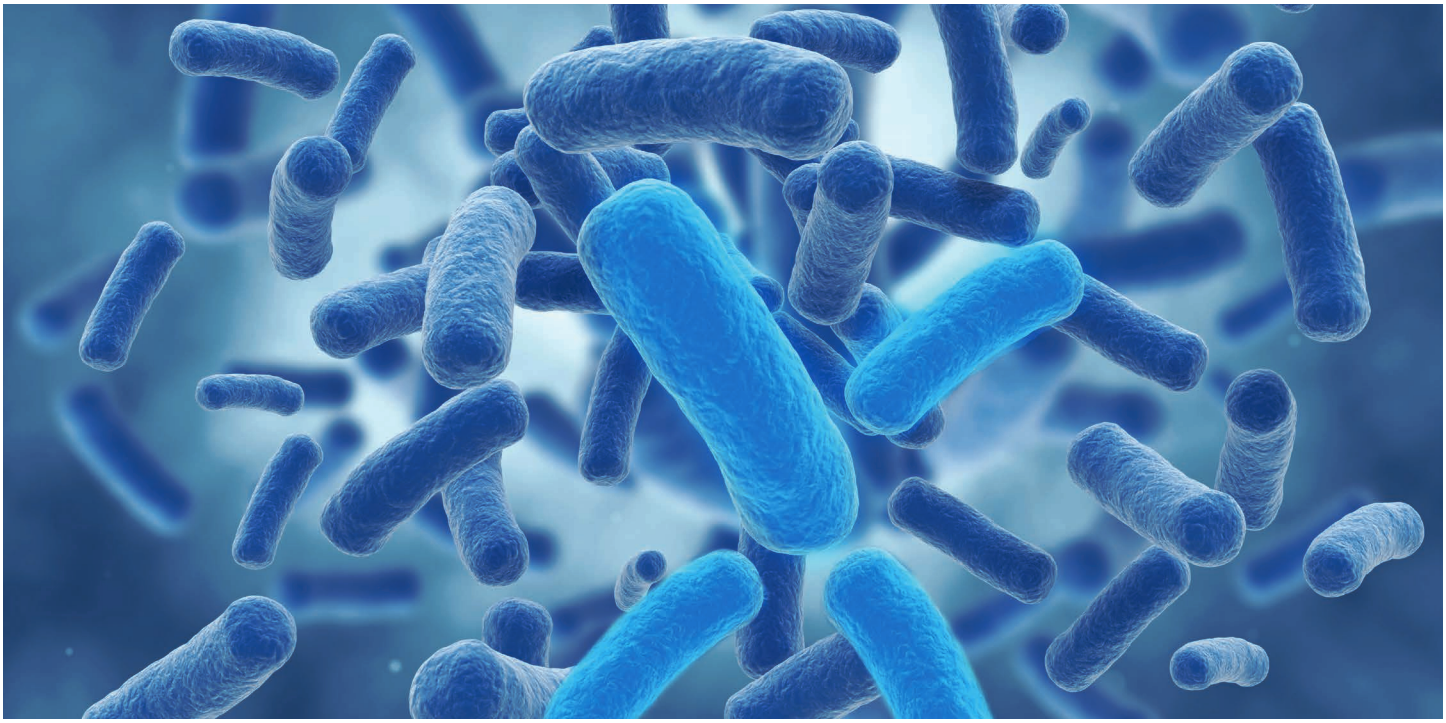
Study Implementation Challenges

- **Research objectives versus clinical care objectives:** In terms of implementation challenges, the key is to understand that the rate-limiting factor is not going to be patients. It's going to be both site and patient burden.
- **Variability in patient population and standard of care:** These patients are very sick, and their management is going to be dictated by the local standard of care. Avoiding dictating or negotiating with centers in terms of what is feasible or changes to the current practice is paramount. It is more important to be able to recruit patients and to keep them in the trial.
- **Standardization of supportive care:** Supportive care is standardized institution-by-institution, and it's going to be managed by multiple players at the site level. If a Sponsor tries to change those practices, they're not likely to be successful.
- **Size and multidisciplinary nature of the study team:** Training of the team is paramount, and training of the broader team is even more important.
- **Team rotation:** Training needs to be repeated because teams rotate on a regular basis. Make sure that whoever is on the floor is aware of the study not only in terms of enrollment but in terms of practices.
- **Personnel and patient burden:** Anything Sponsors can do to limit the personnel and the patient burden will help recruitment and retention in the trial.

Key Data Considerations

- **Stratification(s):** Sponsors will want to have stratifications based on the primary outcome of the trial, but don't stratify too much to have so many cells that the data are confounded. Stratifying by site or at least by country probably is helpful to adjust for the local standard of care.
- **Morbidity index:** Measuring some type of morbidity index in immunocompromised patients that have a high likelihood of mortality is paramount to adjust the analysis.
- **Adjudication committees or central read:** Having adjudication committees or central reads of various imaging or procedures is important to adjust for local practices and diagnosis.
- **High volume of AEs and SAEs:** Expect high volumes of AEs and SAEs in the immunocompromised patient population and try to streamline how those can be reported to consolidate the interpretation of data and the work from the site.
- **Mortality attribution:** Having mortality attribution is a very difficult exercise that should be thought about early on. Those patients typically have more than one cause of death and attributing it to infection versus something else may or may not be feasible and a committee may just not be that helpful.
- **Judicious concomitant medications collection:** Concomitant medications are numerous in the immunocompromised. Defining what is collected and what is not needed, as in the standing PRN orders in those patients, will be important.
- **Multivariate analyses:** Expect to do a lot of multivariate analyses to adjust for different factors and look at specific subpopulations in those patient populations.

Dr. Herve Mommeja-Marin and Dr. Anibal Calmaggi share more insights on infectious diseases in the immunocompromised host in an on-demand webinar available on Medpace.com.



FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical, and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.

REFERENCES AND SUGGESTED READINGS

1. Danby R, et al. Front. Immunol., 24 February 2014 | https://doi.org/10.3389/fimmu.2014.00068
2. Schuster MG, Cleveland AA, Dubberke ER, et al. Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study. Open Forum Infectious Diseases. 2017;4(2):ofx050. doi:10.1093/ofid/ofx050
3. Mikulska M. J Infect 2014;68 (4): 321-31
4. KOH A. PLoS Pathog. 2017 Jun 29;13(6):e1006342. doi: 10.1371/journal.ppat.1006342
5. Tiera et al, Blood, 2016
6. Hill et al, Blood, 2017
7. Zerr D et al, Blood, 2011