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Q1 CAR-T cell therapy has shown immense promise in treating cancers, but its cost remains a barrier for many patients. What do you think can be done to make CAR-T therapy more affordable and accessible to a larger patient population?

Chabannon: We will be in a good position to take action when we better understand cost structures that are associated with the clinical use of CAR-T cells. As expensive as it can be, the cost of acquisition of the medicinal product is only one component. Hospital infrastructures and organisations that are needed for safe and efficient administration also account for a significant share of the cost. Moreover, CAR-T cells are administered as salvage therapies, and one has to consider the cumulated costs of treatments that were administered prior to the infusion of CAR-T cells.

Now manufacturing costs only account for a fraction of the face value of a medicinal product. While manufacturing advanced therapies is way more expensive than manufacturing conventional drugs or biologicals, it still accounts for a fraction of the cost. Other determinants include research and development costs, accounting for all medicinal products that failed during development and the need to recover associated costs, as well as the perception that the price of treatment may, more or less, equal the cost (and thus savings) of standard-of-care for the same indication.

Campodonico: Regarding the accessibility and affordability of CAR-T cell therapy, I mostly agree that the cost of the drug is just one part of the overall treatment expense. The total cost is quite high, especially when considering hospitalisations and the treatment of various complications, which place a significant burden on healthcare systems. To expand the scale of this treatment, in addition to what Christian mentioned, there are some interesting tools, particularly the promotion of academic CAR-T cell therapies. This is an important topic, as academic protocols offer quicker and relatively cheaper products, making them a valuable alternative to standard treatments. These should be encouraged worldwide, as we've seen in examples from Spain and Israel. Some colleagues within EBMT have already paved the way for such treatments, which can complement standard care products and help reduce the costs of external manufacturing. This is an important point to consider. Ultimately, much of the work needs to be done at the level of national healthcare systems. Harmonisation is essential, especially among the various countries that are members of EBMT. In this regard, healthcare authorities should ensure that CAR-T cell therapy is appropriately utilised and implemented, always respecting indications, so that resources are efficiently allocated.

Q2 From a healthcare systems perspective, what are some strategies that could help reduce the financial burden of CAR-T therapies while maintaining their effectiveness?

Chabannon: While the marketing approval is issued at the European level by the European Medicines Agency (EMA), reimbursement is decided at

the national level by Health Technology Assessment (HTA) agencies; harmonisation is further needed in this field. Decreasing the costs of manufacturing through decentralised (point-of-care) manufacturing and the introduction of improved automated engineering techniques and devices are potential ways to decrease costs to the healthcare system, for as long as safety and efficacy are comparable to those measured with commercial CAR-T cells. From this viewpoint, the ongoing comparative trial that is ongoing in the Netherlands with the HOVON cooperative group will produce important information.

Q3 How can we balance the rapid development of CAR-T therapies with ensuring long-term safety and effectiveness for patients?

Chabannon: CAR-T cells are living drugs and may elicit long-term clinical activity, whether favourable or unfavourable, that cannot be detected in registration trials. Thus, the need for high-quality registries that capture long-term follow-up of CAR-T cell treated patients. The recent reports of T cell lymphomas arising in patients treated on both sides of the Atlantic, some of them with detection of the CAR sequence in lymphoma cells, led to promptly re-examining the risk–benefit ratio of CAR-T cells. The rarity of these adverse events is such that the benefit of CAR-T cell therapies is maintained; however, it rang the bell for specialists in the field. CAR-T cell-treated patients must be followed up for their entire lifetime after treatment.

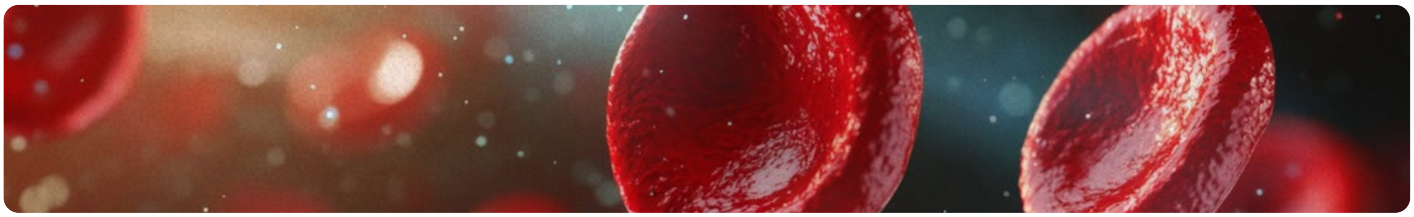
Campodonico: Once again, I believe Christian already highlighted the importance of registries. High-quality registry data is essential, and EBMT does this very effectively, though there's always room for improvement. In times of political instability, it's crucial to avoid over-fragmentation. One key point to remember is the importance of having a centralised registry rather than relying on national ones. A uniform registry with data entries from most centres performing this therapy would enable faster monitoring of severe and unexpected adverse events, which is vital. More generally, adverse event reporting is critical for all practitioners. Additionally, single-centre experiences are valuable, as they help us understand the incidence of specific adverse events, particularly second malignancies. This understanding is essential when determining the emphasis that should be placed on these concerns during patient consultations prior to CAR-T cell therapy.

Q4 Christian, given your involvement with the GoCART Coalition, could you share some background on the initiative and its key objectives?

Chabannon: The GoCART Coalition is an initiative started in 2020, supported both by EBMT and the European Hematology Association (EHA), and was meant precisely to bring all stakeholders around the table to address questions such as costs and affordability, among others. Streamlining the installation of CAR-T cell activities through collective and individual training and qualification is another important avenue.

Q5 Looking ahead, what do you believe is the next major step for CAR-T cell therapy, both in terms of improving patient outcomes and addressing its accessibility and affordability issues?

Chabannon: Without being overly pessimistic, I notice that over the last couple of years, the field has not produced clinical innovations at the same rate as in the years before, particularly if we consider malignant blood diseases and solid tumours. Meanwhile, preclinical developments are blooming, and it is reassuring that European groups and companies are now taking their full share of these



projects. My personal bet would be on *in vivo* reprogramming to generate CAR-T cells; this is a fascinating approach, and some convincing preclinical work has been published in high-profile journals, and early clinical trials recently started.

Campodonico: In terms of improving patient outcomes, I believe the biggest challenge we're facing is extending the CAR-T cell revolution to oncology. While there's much discussion around this, the clinical implementation is lagging behind the promising preclinical data. Currently, the outlook for clinical trials involving solid malignancies remains limited. The expansion and refinement of CAR-T cell therapies, including the addition of new engineering techniques, chimeric stimulator receptors, and combinatorial approaches such as TME modulation, are crucial for breaking through the barrier in oncology and making CAR-T cells applicable to solid tumours.

Regarding accessibility and affordability, a key point is to increase the number of manufacturing facilities. This would ensure that all patients in need of cell therapy can undergo apheresis and benefit from timely product manufacturing. As we know, this is a significant challenge for certain disease indications and geographical regions. By expanding the number of accredited centres for CAR-T cell production, we can improve accessibility for more patients.

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Q6 As CAR-T therapies become more widely used, how do you envision collaboration between clinicians, researchers, and healthcare policymakers to ensure that advancements in CAR-T therapy are both innovative and accessible to all patients who could benefit from them?

Chabannon: The question obviously covers a much broader field than CAR-T cells and immune effector cell-based therapies, and resorts to the balance in public and private expenses dedicated to healthcare in countries with defined gross domestic products. EBMT "historical business", i.e., haematopoietic cell transplantation remains unequally accessible in low-, middle-, and high-income countries after more than 5 decades of medical practice. My expectation is that the same will happen for CAR-T cells, although the hierarchy of low-, middle-, and high-income countries is likely to change on a global scale in these times of political turmoil, and that mitigating inequalities in access requires collaboration and consensus building across all stakeholders: this is essentially the GoCART Coalition mission. CAR-T cells provide a paradigmatic example of a day-to-day collaborative effort that involves healthcare practitioners and institutions along with providers of medical goods; this needs to be reproduced at a global level where managing decisions can be built.

Campodonico: I think it's crucial to have a strong integration between basic researchers and clinicians within tertiary care centres. This is a point that cannot be emphasised enough. From personal experience, I've seen that this communication is often lacking in many centres, where the scientists designing the products don't always engage with the clinicians who will ultimately apply and test these products in humans. On a smaller scale, it's vital that any centre aiming to design new cell-based products foster multidisciplinary collaboration between clinicians and basic researchers.

On a broader scale, this also requires cooperation within scientific societies like the EBMT, and it's especially beneficial to focus on meetings that take a translational approach. For example, the CAR-T cell meeting is a perfect interface where researchers and clinicians come together, giving them the opportunity to discuss and exchange ideas on the latest developments in the field. These kinds of events play a key role in bridging the gap between research and clinical practice, helping to drive the field forward.