

REVIEW ARTICLE

Challenges of Initiating Gene Therapy Medicines for Cancer in UK Hospital Pharmacy

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ABSTRACT

Cancer is a complex and multifactorial disease which can be associated with both genetic and environmental abnormalities. Gene therapy medicines are classified as advanced therapy medicinal products (ATMPs). The use of ATMPs in cancer is a new era in medicine, which requires the support from specialist and experienced staff and the regulatory authorities to introduce gene therapy medicines safely and effectively into clinical practice.

In Europe, the European Medicines Agency (EMA) has approved a Gene therapy Medicinal Product (GTMP), Talimogene Laherperepvec (Imlygic) for melanoma, a Cell Therapy Medicines Product (CTMP), Zalmoxis for patients with haematopoietic Stem Cell Transplantation (SCT) and two Chimeric antigen receptor T-cell therapies (CAR-T cells), Tisagenlecleucel (Kymriah) and Axicabtagene ciloleucel (Yescarta), for the treatment of acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL).

Regulatory authorities, expert members in this field, and experience from clinical trials have come together to build guidance and provide advice on how to initiate these novel therapies in clinical practice. Risk assessments and standard operating procedures should be in place before gene therapy is introduced in healthcare centres. Gene therapy in cancer is an exciting new era, with challenges for healthcare professionals to implement, manage and monitor this new group of therapy. Clinical exposure and extensive research have provided a deeper understanding and improvement of medicines optimisation and safety. Scientific and safety challenges are being explored and answered in clinical trial settings, with safety precautions always being paramount to ensure the efficiency and the safe delivery of these therapies. In this review, we will summarize the gene therapy medicinal products that are licensed in the UK and the challenges that need to be taken into consideration before hospital pharmacy initiates those therapies in clinical practice.

Introduction: Cancer is the second leading cause of mortality globally, estimated at 9.6 million of deaths in 2018. It is a complex and multifactorial disease which can be related to both genetic and environmental abnormalities (WHO, 2018). Gene therapy medicines are classified as advanced therapy medicinal products (ATMPs). The use of ATMPs in cancer has introduced a new era in medicine, which requires the support from specialist and experienced staff and the regulatory authorities to introduce gene therapy medicines safely and effectively into clinical practice. Gene therapy medicines substitute a malfunctioning gene by introducing a functional or a missing gene, to correct an abnormal underlying disorder, or introduce a gene that can induce a therapeutic pathway (Friedmann, 1992, NIH, 2017). In the *Journal of Gene Medicine* published in 2017, 65% of gene therapy clinical trials were in cancer (n=1688) (Ginn et al., 2018), placing cancer at the top of gene therapy clinical trials compared to other diseases since the previous review in 2012 (Ginn et al., 2013). In addition, it was shown that the rate of gene therapy trials in phase II, II/III and III has increased significantly over 5 years (Ginn et al., 2018), indicating that safety has been determined and many therapies are moving towards marketing authorisation procedures.

Gene therapy in cancer is considered beneficial over chemotherapy because it involves a targeted treatment against cancer cells without the chemotherapy adverse effects. Moreover, it is considered the ultimate challenge in cancer, which can provide a long-term therapeutic benefit or

optimal cure. Many different pathways related to genetics in terms of diagnosis, prevention and treatment of cancer are being researched. The EMA has provided marketing authorisation in Europe for a GTMP, Talimogene Laherperepvec for melanoma and a CTMP, Zalmoxis for patients with haematopoietic SCT (EMA, 2018b, EMA, 2018c) (Table 1). The EMA has approved two CTMP, CAR-T cells, Tisagenlecleucel and Axicabtagene ciloleucel for the treatment of ALL and DLBCL (EMA, 2018a) (Table 1). The National Institute of Health and Care Excellence (NICE) approved Talimogene Laherperepvec in 2016. Tisagenlecleucel and Axicabtagene ciloleucel have been recommended by NICE under the Cancer Drugs Fund program in England in 2019 (NHS, 2019a).

The oncology ATMP, Talimogene Laherperepvec, is an oncolytic immunotherapy derived from herpes simplex virus type 1 (HSV-1), which is approved for the treatment of advanced melanoma (EMA, 2018b). Talimogene Laherperepvec is the first approved modified HSV-1 which produces a human granulocyte-macrophage colony-stimulating factor (GMC-SF) that leads to cell apoptosis. It is injected intratumourally, cutaneously, subcutaneously and into the nodal lesions which are detectable via ultrasound, causing an immune response (SPC, 2018). The OptiM trial, is a phase III multicentre study, where 16.3% of patients administered Talimogene Laherperepvec had a durable response rate, with 10.8% showing complete response and 15.6% partial response. Median overall survival

was 23.3 months in Talimogene Laherperepvec compared to 18.9 months on the control group. Most common adverse effects included tiredness, temperature, sickness, influenza-like disease, cellulitis, chills and pain in the injection site, with all of them being mild to moderate. (Andtbacka et al., 2015).

EMA has approved two CTMPs, tisagenlecleucel and axicabtagene ciloleucel for ALL and DLBCL. Tisagenlecleucel is recommended for paediatric patients, younger than 25 years old, for relapsed refractory B-cell ALL and for adults of relapsed or refractory DLBCL who had at least two lines of treatment (EMA, 2018a). Tisagenlecleucel is a CD19+ genetically modified autologous T-cell immunotherapy. It is an individualised treatment, where the cells are extracted from the potential candidate through leukapheresis of white blood cells. First, they are exposed to antibody magnetic beads to encourage T-cell proliferation and then moved to genetic reprogramming. The genetic reprogramming involves a lentiviral vector which encodes the CD19 gene. Ultimately, the tisagenlecleucel CAR-T cells are infused back into the patient. Prior to infusion, the patient undergoes chemotherapy, in order to enable CAR-T cells to proliferate and persist in vivo. Tisagenlecleucel binds to CD19 antigen on the surface of B-cells and activates a signalling cascade which leads to cell death and release of cytokines that improve the expansion of tisagenlecleucel mechanism of action (Vormittag et al., 2018). The latest results from the ELIANA study in 75 infused patient have shown 81% overall

remission rate with three or more months of follow-up, whereas event-free survival and overall survival at six months was 73% and 90%, respectively. In addition, treatment was detectable up to 20 months after administration, indicating long-term persistence of treatment. The main adverse effects are Cytokine release syndrome (CRS) and neurological toxicity. 77% of patients who were administered treatment developed CRS, with 46% being grade 3 and grade 4. 40% of patients who were administered tisagenlecleucel developed neurotoxicity, 13% was grade 3 and no incidence of grade 4. Thirty-five out of the 75 infused patient (47%) were admitted to the intensive care unit (ICU) for management of CRS (Maude et al., 2018).

Axicabtagene ciloleucel is another CD19+ genetically modified autologous T-cell immunotherapy approved by the Food and Drug Administration (FDA) and EMA (EMA, 2018a, FDA, 2017). It is recommended for adults with relapse or refractory DLBCL and primary mediastinal large B-cell Lymphoma who already had at least two lines of treatment. Common side effects include CRS, neurotoxicity, nausea, diarrhoea, hypotension, increased temperature and tiredness. In the ZUMA-1 trial, 101 (91%) individuals were administered axicabtagene ciloleucel with 54% complete response rates. Overall survival was 52% at 18 months. Grade 3 or more of CRS and neurologic events was 13% and 28%, respectively (Neelapu et al., 2017). Zalmoxis is a somatic CTP, approved in Europe for patients who have treatment for haploidentical haematopoietic SCT as a supportive treatment for serious

haematological malignancies. This treatment is administered to improve the patients' immune system by administering genetically modified T-cells with a suicide

gene. It is administered between day 21-49 after the SCT in patients whose immunity is not recovered and in the absence of graft-versus-host disease (EMA, 2018c).

Table 1. Gene therapy medicinal products approved by EMA or FDA

Agent	Licensed Indication	Company/Trial name	Date Approved	Approving Agency
Oncology				
Talimogene laherparepvec (Imlygic)	Unresected, Stage IIIB-IV Melanoma	Amgen/OPTiM	December 2015 / October 2015	EMA/FDA
Haematology				
Tisagenlecleucel-T (Kymriah)	R/R B-ALL R/R DLBCL	Novartis/ELIANA	August 2018 / August 2017	EMA/FDA
Axicabtagene ciloleucel (Yescarta)	R/R DLBCL	Kite/Zuma01	August 2018 / October 2017	EMA/FDA
Zalmoxis	Haematopoietic SCT	MolMed SpA	September 2016	EMA

R/R B-ALL: relapsed / refractory B-cell Acute Lymphoblastic Leukaemia, R/R DLBCL: relapsed / refractory diffuse large B-cell lymphoma, SCT: stem cell transplantation, EMA: European Medicines Agency, FDA: Food and Drug Administration

RISK ASSESSMENT AND STANDARD OPERATING PROCEDURES IN HEALTHCARE

In 2007, the European Association of Hospital Pharmacy produced guidance on how to provide safe handling of licensed gene therapy medicines in the pharmacy in terms of storage, dispensing, administration and disposal of licensed genetically modified organisms (GMOs) (Vulto et al., 2007). The National Pharmacy Clinical Trials Advisory Group together with the NHS Pharmaceutical Quality Assurance Committee have published guidance regarding the role of Chief Pharmacists in ATMPs in terms of responsibilities and governance to oversee every aspect of ATMPs within every organization (NHS, 2017). In the UK, licensed Genetic

Modified Organisms (GMOs) are regulated by the Medicines and Healthcare products Regulatory Agency (MHRA) without the involvement of the Health and Safety Executive (HSE) Guidance on GMOs. Clinical trial GMOs are regulated by the HSE Guidance on GMO's. This demonstrates the importance of governance procedures in the clinical setting. Hospitals should have a specialist Genetic Modification Safety Committee (GMSC) and Technology Advisory Group to assess technical issues before GMOs are initiated in clinical practice (Stoner, 2018, NHS, 2017).

Gene therapy has raised some technical concerns, which need to be assessed prior to initiating treatment in clinical practice. Ideally, hospital pharmacies should have

specific gene therapy medicine aseptic facilities for handling these products. Alternatively, the use of existing aseptic facilities needs to be evaluated dependent on the risk assessment. Freezers are required to store GMO products. These facilities are available in centres which are familiar and experienced with gene therapy medicinal products from clinical trials (Stoner, 2018). Other issues involve the side effects and the delivery system to maximize the safety and efficacy of the GTMP (Das et al., 2015). Most importantly, regulatory and governance procedures need to be in place in order to initiate gene therapy in clinical practice safely, indicating the importance of the role of a clinical pharmacist. In fact, GMOs are considered medicinal products, therefore the pharmacy department is ultimately responsible for every procedure required, highlighting the importance of the Chief pharmacist's role for management of GMOs in the clinical setting (Stoner, 2018). In relation to CAR-T cell therapy, experts from multiple medical centres and medical discipline areas have created the CAR-T-cell therapy associated TOXicity (CARTOX) group to provide advice for the monitoring and management of CAR-T therapy and its toxicity (Neelapu et al., 2018). Specific centres in the UK have been commissioned by the NHS to deliver licensed CAR-T cell therapy (NHS, 2019b).

GTMPs are classified as level 1 or 2 biosafety hazard in Europe. Class 1 is an agent that does not cause any disease and has minimal risk, whereas class 2 is classified an agent of a moderate potential risk of causing disease as per the centre for

disease control (CDC). Class 2 agents usually include replicating vectors, where the safety information and the risk assessment indicates this class of agent (Vulto et al., 2007). The European Directive 98/81/EC, suggests that those two classes do not require isolated laboratory precaution, however, procedures should be restricted to isolated areas to minimise contamination (EUR-Lex, 2018). In fact, procedures for handling gene therapy depend on the process and the level of exposure. Class 1 can be drawn up and administered in the same clinic areas as normal chemotherapy. Class 2 requires additional containment measures to be in place, for example, it could be drawn up and administered in side rooms, with a sign on the door "Do not enter" together with a biohazard sign on the door, unless advised differently by the risk assessment. Some class 2 agents should be reconstituted in specific GMO aseptic facilities. Talimogene Laherperepvec is classified as class 1, hence it can be administered in clinic areas, but institutional guidance should be in place depending on aseptic facilities (SPC, 2018).

In terms of technical issues related to storage and handling, it is important to highlight that some GTMs are cryopreserved and once unfrozen they have a very short shelf-life. Talimogene Laherperepvec needs to be stored frozen between -90 to -70 centigrade and has a specific shelf life when thawed, depending on the temperature and the dose. Therefore, the pharmacist's role is essential to ensure correct storage and handling procedures during all stages of pre and post-treatment. In all cases, specific training for every

GTMP and SOPs should be in place, demonstrating that safety procedures and risk assessments are taken into consideration prior to initiation of GTMPs in clinical practice. Furthermore, aseptic facilities should be in place to ensure safe reconstitution and administration of ATMPs dependent on the class and risk assessment (Stoner, 2018).

As for CAR-T therapy, tisagenlecleucel and axicabtagene ciloleucel are under the Risk Evaluation and Mitigation Strategies (REMS) program by FDA and Prime program by EMA in order to ensure that safety concerns are mitigated and the benefits of treatment outweigh the risks (EMA, 2019, FDA, 2019). The main purpose of these programs is to provide support and training to introduce ATMPs safely and effectively in clinical practice. Every healthcare centre and member of staff responsible for prescribing, administering or handling this therapy should undertake appropriate training prior to initiating CAR-T therapy in the clinical setting, especially in relation to the management of adverse effects related to CRS and neurotoxicity. In addition, specialist support and supportive medicinal care should be available in the event of toxicity such as ICU support or tocilizumab in case of CRS. Patients should also be provided with a Patient Wallet card with close monitoring for at least a month after infusion. All members of staff should be trained and repeat the training if they have not been involved in CAR-T treatment responsibilities for more than a year (FDA, 2017). In Europe, the EMA has provided a Risk Management Plan for those therapies

which are available in the SmPC and the SmPC package leaflet. As tisagenlecleucel and axicabtagene ciloleucel fall under haematology and SCT, the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and the European Society of Blood and Marrow Transplantation (JACIE) have provided accreditation to certain healthcare centres for those therapies. JACIE has a rigorous framework for providing accreditation standards for BMT (Snowden et al., 2017), this has offered the advantage of an existed structure to be applied to ATMPs. In the UK, NHS England together with JACIE and the life science companies have nominated 9 centres for the CAR-T treatment of ALL in children and adults younger to 25 years old and 7 centres for adults with large B-cell lymphoma (NHS, 2019b). The selection was based on the geographical distribution and a scoring system related to ICU access, cell apheresis, pharmacy capacity, Immune Effector Cell (ICE) storage capacity, experience and clinical trial exposure of CAR-T cells. An on-site inspection to assess the facilities, the patient safety, the staff competency and the whole process for delivering high-risk therapies in the clinical setting was performed likewise (NHS, 2019b).

Risk assessment programs have a role to familiarise all the healthcare professionals involved with the management of treatment of these new therapies. The role of the pharmacist is essential in every stage related to ATMPs as they are considered to be medicinal products and therefore are controlled by medicine legislation. It is essential that all healthcare staff, and

especially the pharmacy, should be prepared to engage in gene therapy in clinical practice ensuring that patients' safety and medicines' efficacy is well maintained.

RISKS AND CONCERNS UNDER RESEARCH

In 2014, the NIH recombinant DNA Advisory Committee on the independent review and assessment has raised important concerns related to gene therapy in clinical trials. It was highlighted that not all trials have been completed, leading to essential considerations when research studies are intended to proceed further. Some of the most essential problems involve a poor expression of viral vectors to cause an anticipated response or increased / uncontrolled expression which can lead to side effects and toxicity (Gostin et al., 2014). Nevertheless, further clinical exposure and extensive research have resulted in constant development, deeper understanding and improvement of a general medical framework for medicinal product safety. FDA and NIH Recombinant DNA Advisory Committee (RAC) have concluded that ongoing exposure in gene therapy should facilitate regulatory procedures and exceptional review is required in circumstances where novel gene therapy products are initiated, establishing some criteria to facilitate reviewing clinical trial protocols (Lenzi et al., 2018). Having gained extensive experience with ATMPs, we have reached a point where gene therapy is available and implemented in routine clinical practice. Although scientific and safety challenges are waiting to be explored and answered in a clinical trial settings, safety precautions should be in

place for the efficient administration of those therapies (Collins and Gottlieb, 2018).

Direct gene transmission can activate pharmacological pathways through transgenes, which can increase the risk of treatment or obscure toxicities, unravelling complicated pathways which are unidentified. Another issue related to toxicity is the immune response, highlighting the importance on a public health or occupational health level of action (Kimmelman, 2005). There is also the potential risk of genotoxicity, meaning the ability of gene therapy to cause a response in healthy unaffected cells and lead to toxicity. It is important to consider that the viral vectors may precipitate in other organs of the body such as brain or striated muscles and lead to long-term toxicity (Lee et al., 2013). The risks of gene therapy require detailed awareness of the acceptable risks, to ensure the safety of the patient, third parties who are involved, and the whole population and the environment. This is an estimation of the actual and the theoretical risks under scientific investigation (Lenzi et al., 2014).

Last but not least, ethical issues have been raised, relating to the safety of transferring genetic material in patients and the risks involved in humans. Since gene therapy can act on the host genetic material of the patient and cause amendments in the internal body instructions, the risk and benefit in terms of treatment and the safety of the patient need to be considered. Two main categories include germline gene therapy which is related to the initiation of the functional gene into the reproductive

system and somatic gene therapy where the genes are introduced into somatic cells (Ibraheem et al., 2014). In the UK, gene therapy in the germ cells (reproductive system) is not allowed as per Clinical Trials Regulations 2004 due to a potential risk of passing harmful effects in the future generations (POST, 2005).

Conclusion

Cancer is a complex disease and many therapeutic pathways need to be taken into consideration on a genetic level. Genes which enhance cell proliferation or suppress tumour expression leading to apoptosis are the major pathways where their counterbalance could cause cancer. Hence, genes acting against oncogenes or genes causing apoptosis can be used for the therapy of cancer (El-Aneed, 2004). The idea of delivering a modified gene into the circulation to correct a pharmacological pathway or to produce an immune response is promising. However, more awareness and understanding is required to improve those treatments, having as a priority the risk-benefit of the disease and the safety of the patient. Gene therapy in cancer is an exciting new era, with challenges for healthcare professionals to implement, manage and monitor this new group of therapies. Clinical exposure and extensive research have provided a deeper understanding and improvement of the general medical framework for medicinal product safety. The UK has developed guidance for pharmacy staff to ensure the appropriate and safe handling of this new generation of medicines that are being implemented in the clinical setting. Scientific and safety challenges are waiting

to be explored and answered in the clinical trial setting, with safety precautions always being paramount to ensure the efficiency and safe delivery of these therapies.

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