Cell therapy shows promise in pancreatic cancer

Pancreatic ductal adenocarcinoma is notorious for its poor patient prognosis, with five-year survival at less than 10%. While the field is progressing fast, and new combination therapies, such as gemcitabine and capacitabine, and FOLFIRINOX, have extended survival rates, most patients develop tumour recurrence within five years and even after surgical resection, long-term survival is rare.

Several clinical studies have assessed checkpoint inhibitors like PD-1 in pancreatic cancer, but with limited efficacy observed to date. The lack of efficacy of checkpoint inhibitors can potentially be explained by T cell dysfunction and exclusion, a recognised characteristic of non-immunogenic 'cold' tumours such as pancreatic cancer.

In this article, we discuss a cell therapy approach that could be a powerful mechanism for inducing T cell responses to pancreatic cancer, either as a monotherapy or in combination with checkpoint inhibitors. Our review is based on an analysis of the first cohort of patients in an ongoing clinical study called REACtiVe. An analysis of the first cohort of 10 patients treated with Amphera's therapy, MesoPher, was published on 28 April 2022 in the *European Journal of Cancer*. All of the patients had resected pancreatic cancer and had completed standard-of-care chemotherapy.

This study, and the clinical and translational data it has generated, looks at the use of dendritic cells (DCs) in pancreatic cancer. Specifically, it evaluates the MesoPher technology, which is comprised of autologous dendritic cells loaded *ex vivo* with an allogeneic tumour-cell lysate containing a broad repertoire of tumour-associated antigens. Called PheraLys, the lysate is comprised of a number of clinical grade mesothelioma cell lines, which have been extensively tested and characterised. These stable cell lines ensure an inexhaustible source of tumour cell derivatives of constant quality. While PheraLys was developed with mesothelioma cell lines, these cell lines share numerous antigens with pancreatic tumours.

We believe that MesoPher, using the PheraLys lysate, has several potential advantages over other methods of loading dendritic cells. As an off-the-shelf product, PheraLys eliminates the need for autologous tumour material, a logistical hurdle as it can be complex to obtain. By comparison, dendritic cell immunotherapy, with a broad antigenic repertoire, decreases the possibility of tumour escape by eliciting a broad T cell response.

How has MesoPher performed in the clinic to date? The 10 patients in the first cohort of the REACtiVe study received three bi-weekly injections of MesoPher and booster injections at four and seven months. The main objectives of the study were to assess feasibility, safety and immunogenicity of the therapy. Other objectives included progression-free survival, and overall survival.

The study investigators found the MesoPher therapy to be feasible for all patients. All batches of the therapy passed quality and sterility controls, and the administration of the product was also successful. On the safety front, all patients experienced some injection site reactions, including rash, itchiness and soreness, and low grade infusion-related reactions, including chills, fatigue, fever, headaches and vomiting. However, no serious adverse events related to MesoPher were observed.

As part of the research, the investigators explored the presence of shared tumour-associated antigens between MesoPher and pancreatic cancer. While PheraLys has a broad repertoire of tumour-associated antigens, central to its functionality is the ability to prime dendritic cells with antigens shared with the target tumour. The investigators used two approaches to assess this commonality. As a first approach, they observed the mRNA expression of known tumour antigens in PheraLys and in the patient tumours. A total of 111 tumour antigens were detected, 42 of which were shared between PheraLys and patient tumours. Secondly, at a protein level they observed 51 known tumour antigens, of which 39 were shared between PheraLys and the patient tumour.

Taking this analysis one step further, the research team investigated a critical component of the proposed mode of action of MesoPher: does MesoPher induce T cells against the tumour of the patient?

The lead investigator for the trial, Casper van Eijck, and co-author of the paper in the *European Journal of Cancer* has noted that through an elegant *in vitro* co-culture assay using CD137 as a marker for tumour antigen specific T cells, the team was able to show that MesoPher vaccination induced CD4+ and CD8+ T cells that were able to respond to autologous tumour lysate-loaded dendritic cells. This indicates that MesoPher not only induces a T cell response in pancreatic cancer patients, but that the T cell response is tumour specific. We regard this as interesting evidence for our proposed mode of action for MesoPher and its ability to overcome the immune suppression that characterises a cold tumour.

Worthy of note, this latest REACtiVe data, albeit in a small cohort of 10 patients, has yet to reach median progression-free survival or overall survival, as seven of the 10 patients had not shown disease recurrence at the 25 month cut-off time period of the analysis. Furthermore, the three patients with disease recurrence did not demonstrate rapid tumour growth. The expansion cohort of 28 patients in the REACtiVe study is expected to report top line data at the end of 2022.

Joachim Aerts, the inventor of MesoPher and medical advisor to Amphera, has observed that the ability of MesoPher to induce T cell reactivity to the tumour of the patients, first demonstrated in a Phase 1/2 study in mesothelioma and now in this pancreatic cancer setting, has the potential to open new avenues in the treatment of these types of cancer. Indeed, with MesoPher opening the door to cold tumours, combination therapies with checkpoint inhibitors could provide even greater potency and efficacy. Moreover, in the fourth quarter of this year, we expect the read-out of a Phase 2/3 study with MesoPher in mesothelioma.

This article was prepared by Rob Meijer and Ilona Enninga, respectively CEO and COO of Amphera BV.