Commentary: Erik Manting

The role of relapse vaccines in fighting cancer

Perhaps the most clinically problematic characteristic of tumour cells is their tendency to 'go dark' and evade recognition by the immune system by deploying an array of molecular tricks. Even after being pushed into remission by initial treatment, undetected residual cells remain tenacious and often re-establish themselves within a few years, or even months.

But what if these cells could be stripped of their ability to stay hidden and be swiftly cleared by the immune system, as most other early tumour cells are on a daily basis? This is a key question for modern oncology and has become an area of substantial investigation for many companies, including our own concern DCprime in the Netherlands. At the heart of our scientific enterprise is the development of a new class of oncology treatments called relapse vaccines. By providing the immune system with the tools to uncloak and eliminate residual disease before it leads to a clinical relapse, these vaccines offer a new therapeutic paradigm in the treatment of cancer.

A key underlying principle of relapse vaccines is that they are administered when tumour burden is low, following initial treatment such as chemotherapy and, in solid tumours, surgery. This has two main advantages. First, the immune system has a better chance of preventing tumour formation by clearing out residual tumour cells instead of battling an established tumour that comes with physical barriers and a suppressive immune environment.

Second, tumours have the ability to disturb the immune system in multiple ways, including T cell exhaustion, reduced antigen presentation and the triggering of immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells. All of these elements send the immune system into an even more dormant, or tolerogenic, state to the point where it is no longer able to mount an effective immune response. A strong reduction of the tumour burden by chemotherapy takes away the root cause of this immune suppression. And while it is widely believed that chemotherapy inevitably weakens the immune system, it turns out that especially the reduction of immunosuppressive cells results in an immunological 'reset' with often improved immunity as a result. It is in this therapeutic window shortly after initial treatment, that relapse vaccines boost anti-tumour immunity, assisting the immune system in regaining control over the tumour (please see figure 1).

These new insights into the relapse vaccine window are driven by the tremendous number of studies that have been carried out in the field of immuno-oncology in recent years. They have not only yielded breakthrough successes such as checkpoint inhibitors and chimeric antigen receptor T cell (CAR T) therapies but have also demonstrated that tumours remain quite resistant to many therapies due to their ability to block, blunt, or evade the immune responses directed towards them. To tip the balance in favour of the immune system therefore requires a destruction of the tumour by the initial treatment, followed by relapse vaccination to boost anti-tumour immunity leading to deeper and more durable clinical responses.

The relapse vaccine window has long been ignored due to the assumption that it is challenging to define clinical endpoints related to the time to, or probability of, tumour recurrence. However in certain tumours the time to relapse is relatively fast, in the order of months to a few years, and affects the majority of patients and therefore overall clinical outcome. In addition, it has become more feasible to measure residual disease, creating a new opportunity to assess efficacy of new therapeutic approaches that specifically address residual disease, including relapse vaccines.

Consider acute myeloid leukaemia (AML), a highly aggressive cancer of the blood. While partial and even complete remission is frequently achieved following chemotherapy, this tends to be only a brief respite for patients most of whom subsequently relapse, resulting in an overall five-year survival rate in adults of only 27%. In patients above the age of 60 years, the outcome is even worse, with only 15-20% remaining leukaemia-free after two years.

Despite increasing options to achieve clinical remission, the presence of measurable residual disease (MRD) is persistent in many patients and this correlates strongly with the risk of relapse and a relatively short time to progression in AML patients. Measurable residual disease therefore presents a new therapeutic challenge and at the same time, allows for a monitoring of therapeutic interventions aimed at treating residual disease. It is noteworthy that Amgen Inc's bispecific antibody blinatumomab became the first therapy approved by the US Food and Drug Administration for its impact on measurable residual disease in acute lymphoblastic leukaemia (ALL), underlining the clinical importance of this marker in haematological malignancies. To address the treatment of measurable residual disease in the post-remission window in AML, DCprime is developing a relapse vaccine approach.

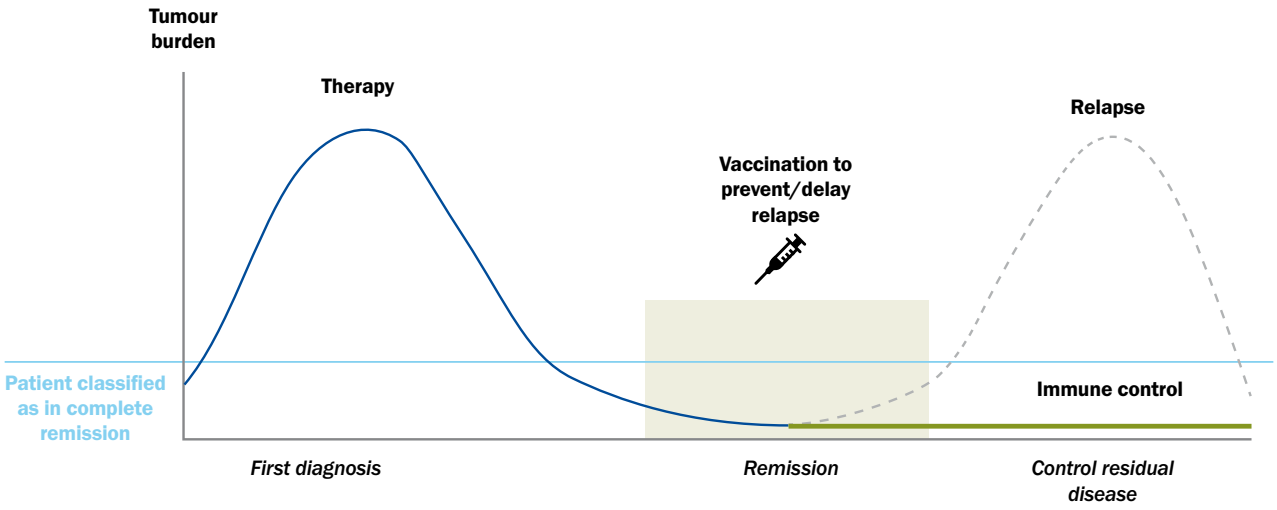
An optimal relapse vaccine boosts the different constituents of the immune system and results in an immune response against multiple tumour antigens, a so-called multifunctional immune response. The relevance of this principle is that tumour cells can escape from the immune system via different mechanisms, for example by shutting down the production of particular antigens or by blocking the presentation of antigenic sequences on their cell surface. Countering immune escape by tumour cells requires immune responses that are directed towards multiple antigens and which involve both cellular and antibody responses.

A relatively straightforward path to developing potent vaccines that trigger multifunctional immune responses is an attenuated version of the actual disease-causing agent. This approach has been successfully followed for many viral and bacterial vaccines, including measles, mumps and typhoid vaccines. Cancer cells however are poor candidates for this approach due to their inherent low immunogenicity. To develop vaccines based on cancer cells would therefore require methods to make them more immunogenic.

© 2019 Evernow Publishing Ltd

Figure 1

Relapse vaccine window in cancer treatment



Source: DCprime BV

This can be done by using biological pathways developed by the orchestrators of the immune system: dendritic cells (DCs). Mixing the phenotype of cancer cells with that of dendritic cells allows for the development of vaccines that combine a broad array of tumour antigens carried by the tumour cells with the immunogenic properties that are inherent to dendritic cells. This approach has been pioneered by researchers at the VU University Medical Center, now Amsterdam UMC, and provided the basis for DCprime as a company.

At the heart of DCprime's approach is the leukaemic DCOne cell line, which was discovered by VU Medical Center researchers. A unique aspect of the cell line is that it can be grown in large quantities and shifted towards a dendritic phenotype in a standardised manufacturing process, providing the basis for off-the-shelf vaccines. The final vaccine product consists of frozen cells, treated with high-dose radiation. The frozen vaccines are shipped to the hospital on demand, where they are thawed at the bedside and administered via intradermal vaccination.

The vaccination has been shown to induce broad immune responses against multiple tumour-associated antigens. Compared with alternative treatments such as maintenance chemotherapy or haematological stem cell transplantation (HSCT), relapse vaccination has a relatively benign safety profile, with the main product-related side effect being redness of the skin around the vaccination area.

Our lead candidate, DCP-001, targets the remission window in AML patients following initial treatments such as chemotherapy. A Phase 1 trial in 12 elderly AML patients at high risk of relapse concluded in 2013 and successfully achieved its primary endpoints of safety and feasibility, including the observation of multifunctional immune responses.

Long-term follow up revealed that in patients that were in complete remission at the time of vaccination, the median overall survival was 36 months, with the longest survival being six years (71 months) after vaccination. Based on these promising data, DCprime has engaged in an ongoing international Phase 2 trial aimed at treating 20 measurable residual disease positive AML patients in the post-remission window. Complete enrolment is expected in 2020, after which the effects of the vaccine on the immune response, measurable residual disease levels, time-to-relapse and overall survival will be evaluated.

Beyond AML, DCprime is developing a broader pipeline in both blood-borne and solid tumour indications that are characterised by the presence of a suitable remission window. Ovarian cancer for instance, like AML, is often driven into remission by initial treatment only to subsequently re-emerge in a harder to treat form in the majority of patients. In such cancers – where there's a high unmet need for treatments that can tip the balance in favour of the immune system to prevent tumour recurrence – relapse vaccines hold significant therapeutic promise.

Conclusion

In summary, a wealth of new insights into the power struggle between the immune system and the tumour have led the clinical community to reconsider and reinterpret many of the old treatment paradigms in oncology. A revolution is taking place in the clinical landscape to monitor and evaluate residual disease, opening up a novel toolbox to zoom in on the post-remission setting.

All of these elements have opened up a new therapeutic window in which relapse vaccines could provide a meaningful way to re-establish a long-lasting immune control of the tumour, with the ultimate aim of extending phases of remission and allowing more patients to avoid subsequent rounds of chemotherapy or other aggressive therapeutic interventions during their lifetime.

This article was written by Erik Manting, PhD, chief executive officer of DCPrime BV in the Netherlands.

© 2019 Evernow Publishing Ltd