Are radio- and chemotherapy effective immunotherapy for cancer?

Immune-modulating cancer therapy – back to the future

Medical writings dating back to the days of ancient Egypt have described spontaneous regression of cancer as a result of what we interpret today to be incidental immune stimulation (1). We can now use new, immune-modulating drugs to target biological mechanisms we have not previously employed therapeutically – or have we? In my view, these drugs will find their place in multimodal cancer therapy, i.e. combined with radio- and chemotherapy. This will widen the indication range to encompass large oncological patient groups.

Oncoimmunological mechanisms are complex. The tumour cells in a solid tumour are interspersed with microvasculature and immune cells in the tumour stroma. The immune cell component consists of a mixture of cell types that suppress the immune activity targeting the tumour, and cytotoxic T-lymphocytes that may attack tumour cells (2). As a rule, the immune cell subsets that protect the tumour are dominant. Cytotoxic T-cells are inhibited because they express a receptor, the programmed cell death 1 (PD-1) protein, which suppresses the cells' signalling when the ligand protein PD-L1 binds to the receptor. PD-L1 is present on the surface of the tumour cells and thus generates an effective defence against cytotoxic T-cell activity.

Two approved therapeutic antibodies, nivolumab and pembrolizumab, block the PD-1 receptor, thereby unleashing cytotoxic T-cells from their binding to PD-L1 (3). The principle is called immune checkpoint blockade. Drugs that target other immune checkpoint factors have also been approved or are in late-phase clinical trials. At the time of writing, approved immune-modulating drugs (ipilimumab, nivolumab and pembrolizumab) are being used as single-agent therapy or in combination for advanced disease from immunogenic tumours, i.e. cancer with inherent immunity, such as malignant melanoma or renal cell carcinoma. Adverse effects are primarily immune-related and may arise from any organ system. We have been learning from clinical experience how to deal with adverse effects, and PD-1 inhibitors in particular are regarded as having relatively low toxicity and thus being safe (4).

But what about cancer diseases that are not particularly immunogenic? Can tumour-targeting immune activity be created so that large patient groups can benefit from immune-modulating therapy? Manipulation of cytotoxic T-cell activity is an area on which many high-tech research centres are concentrating. One example is therapeutic cancer vaccines, which still present a number of unsolved technical and clinical challenges (5). Another example, adoptive T-cell therapy, entails the genetic modification of the patient's lymphocytes after isolation and expansion ex vivo prior to reinfusion (6). Because of the lack of tumour specificity, considerable toxicity has been observed in association with this approach. The first study of metastatic colorectal cancer was terminated after the first three patients developed life-threatening colitis (7). Norwegian researchers recently used experimental models to demonstrate that T-cells from healthy donors can be modified to generate immune activity against another person's tumour cells (8). It is hoped that allogenic T-lymphocytes of this type will not attack the patient's normal tissue.

Technologies that manipulate T-cell activity ex vivo are thus resource-intensive. Are there easier ways of creating tumour-targeting immune activity? Are any such strategies cost-effective (disregarding the exorbitant price of immune-modulating drugs), well tolerated and simple to administer clinically?

Cell death due to radio- or chemotherapy releases tumour antigens, which are captured by antigen-presenting dendritic cells and displayed to cytotoxic T-cells. The phenomenon is called immunogenic cell death. A PD-1 inhibitor may enhance the activation of the T-cell clones, which will then attack disseminated tumour manifestations. An immune-modulating drug in combination with radiotherapy may thus invoke a therapeutic response outside the radiation target volume, known as an abscopal (*ab scopus*; away from the target) effect (9). It has been maintained that in this way radiotherapy is systemic cancer therapy (9).

Well established, inexpensive chemotherapeutic agents may also generate immunogenic cell death. In a study of locally advanced rectal cancer, we administered oxaliplatin-based chemotherapy prior to radiotherapy and surgery and observed unexpectedly good long-term results. Patients in whom circulating, immune-stimulating factors were induced by oxaliplatin appeared to acquire protection against the development of metastatic disease (10). We now intend to study whether the addition of a PD-1 inhibitor to oxaliplatin-based chemotherapy may improve the therapeutic response in established metastatic colorectal cancer.

Radio- and chemotherapy remain the cornerstones of oncology. Thus, we have always applied immunological mechanisms in the treatment of our patients, but without realising it. With the new knowledge we now have a rationale for testing multimodal immune-modulating treatment, in principle on all cancer diseases.

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The author has completed the ICMJE form and reports no conflicts of interest.

References

1. Hoption Cann SA, van Netten JP, van Netten C et al. Spontaneous regression: a hidden treasure buried in time. Med Hypotheses 2002; 58: 115–9.
2. Whiteside TL, Demaria S, Rodriguez-Ruiz ME et al. Emerging opportunities and challenges in cancer immunotherapy. Clin Cancer Res 2016; 22: 1845–55.
3. Felleskatalogen. Opdivo. http://felleskatalogen.no/medisin/opdivo-bristol-myers-squibb-598110 (6.9.2016).
4. Boutros C, Tarhini A, Routier E et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016; 13: 473–86.
5. Melero I, Gaudernack G, Gerritsen W et al. Therapeutic vaccines for cancer: an overview of clinical trials. Nat Rev Clin Oncol 2014; 11: 509–24.
6. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. Science 2015; 348: 62–8.
7. Parkhurst MR, Yang JC, Langan RC et al. T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. Mol Ther 2011; 19: 620–6.
8. Strønen E, Toebes M, Kelderman S et al. Targeting of cancer neoantigens with donor-derived T cell receptor repertoires. Science 2016; 352: 1337–41.
9. Sharabi AB, Lim M, DeWeese TL et al. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. Lancet Oncol 2015; 16: e498–509.
10. Meltzer S, Kalanxhi E, Hektoen HH et al. Systemic release of osteoprotegerin during oxaliplatin-containing induction chemotherapy and favorable systemic outcome of sequential radiotherapy in rectal cancer. Oncotarget 2016. E-publisert 26. april 2016.