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 phenomenon is called immune oncolysis. The tumour 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.

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References