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Editorial

Immunotherapy, where are we going?

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EDITORIAL

After many years of comprehensive research of the cancer immunity cycle, immunotherapy is getting more established and is rapidly emerging as a powerful weapon. It is a biologic therapy helping the immune system to fight the malignancy based on the tumor microenvironment. Immunotherapy includes monoclonal antibodies, cytokines, treatment vaccines, immune check point inhibitors and adoptive cell transfer. It defines a therapeutic era in the field of oncology with different mechanisms of action compared with cytotoxic and targeted therapies, as well as specific secondary side effects and related toxicities. The ways of radiological response assessment are even different: immune related morphological and metabolic criteria were defined. Immunotherapy is the only domain where an increase in the size of a lesion doesn't necessarily mean a progression; this is called "pseudo-progression".

Nowadays, immunotherapy is becoming a standard of care in many tumors either at first line or after progression with drastic improvement in survivals and quality of life. Among these cancers, we can cite: melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer, head and neck squamous cell carcinoma, gastro-intestinal tract carcinomas. Despite all these promising results, the Oncology still lacks the knowledge of who to treat and when to treat. The idea of immunotherapy was initially based on tumor mutational burden, with a direct correlation between mutational load and response to immunotherapy. Then, the principles of tumor infiltrating lymphocytes, dense stroma and immune check point receptors expression got more interest. Unfortunately, most of them remain prognostic, non-predictive factors, and can't be used as surrogate markers for response. Immunotherapy is still used in metastatic settings, but many trials are evaluating its place in neo-adjuvant or adjuvant protocols. Moreover, clinicians are still demanding if it can slow disease progression in case of rapid flare of a generalized disease. Another question under debate is when to stop immunotherapy in responders and at which free interval is it possible to re-challenge upon re-progression.

Knowing that immunotherapy is based on omitting the immune-tolerance of the tumor, many "tricks" have been tried to boost the immune system. These consisted of adding another agent targeting or inhibiting another immune pathway, or via changing the architecture of the tumor microenvironment which is the mainstay of cancerogenesis and tumor dissemination. Thus, many trials showed successful effect of adding chemotherapy or applying radiation therapy (the abscopal effect) on top of the immunotherapy. The main challenge for researchers is how to transform an immune desert media, resistant to immunotherapy to an immune active environment where self-immune cells will be able to fight the tumor cells.

To conclude, it is possible to achieve excellent and durable responses with immunotherapy. It is usually well tolerated despite its broad specific immune related toxicites. Many authors described it as a "tsunami" attacking and devastating the tumor cells all over the body. It is changing the oncologic treatment with the possibility of achieving long term remissions in fatal diseases and positively changing the outcome of many patients. It is a field under ongoing development with many investments trying to answer many questions. The coming years will find the answers after analyzing the ongoing trials. Time will also create, in my opinion, other challenges and may discover new cellular pathways in those who responded or failed the immunotherapy.

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