Immune-related response criteria: light and shadows

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Researchers realised that standard criteria for response assessment are unsuitable for immunotherapy.[1]

They observed that: (1) time to response may be longer for immunotherapy; (2) response may occur after an initial pseudo-progression; (3) discontinuation of treatment may be inappropriate in case of progressive disease (PD) unless PD is confirmed after at least 4 weeks; (4) clinically insignificant PD, such as small new lesions in presence of other responsive lesions, should not be considered and (5) durable stable disease may represent antitumour activity.[2]

Therefore, Wolchok *et al*[2] proposed immune-related response criteria (irRC) to evaluate patients undergoing immunotherapy:

Overall, irRC are based on three main principles:

1. *Tumour burden*: devalues the importance of each target lesion in favour of the whole 'quantity' of disease.
2. *Confirmation*: any response, other than stable disease, requires to be confirmed by a consecutive assessment at least 4 weeks after first documentation.
3. *New lesions*: do not necessarily represent a PD. They must be included into the whole *tumour burden* and their significance is subordinate to the following *confirmation*.

Pseudoprogression represents a risky situation because it may cause treatment to stop.

It must be stressed that among patients showing an early pseudoprogression there are many who will later show major responses (complete response + partial response).[3]

Three hypotheses try to explain 'pseudoprogression'.[2] (1) Homing of cytotoxix T lymphocytes (CTLs) into the tumour following the treatment. Massive infiltration of the tumour by T lymphocytes is demonstrated after treatment.[4] (2) Increase of the inflammatory tumour milieu, which may be induced by (re) activated CTL against tumour cells, which

in turn can induce a transient enlargement of the tumour mass resulting in a pseudoprogression. (3) Fast-growing tumour, which may increase its mass up to a clear progression during the interval between treatment initiation and its biological effect: in this case we should tag the effect as 'transient-progression' rather than 'pseudoprogression'.

The three hypotheses also apply to the development of new lesions during the initial phase of treatment.

They also explain why 'PD', as defined by RECIST and WHO, does not match with immunotherapy.

WEAKNESS OF IRRC

irRC are based on WHO response criteria. The product of the longest perpendicular diameters measures each target lesion. Consequently, tumour burden is the sum of the products of all the target lesions. It accounts for high interobserver variability,[5] at least in clinical practice.

Moreover, measuring tumour burden is time-consuming and it also may represent an issue in clinical practice.

An additional limitation of irRC is that they have been developed based on malignant melanoma treated with anti-CTLA4 or anti-PD-1/PD-L1 monoclonal antibodies (mAbs).

Both these drugs favour the clonal expansion of CD4+/CD8+, and promote adaptive response, albeit anti PD-1/PD-L1 act mostly at tumour site. Clonal expansion supports the hypothesis that pseudoprogression may be due to the massive infiltration of the tumour bed.

However, drugs against different targets are under evaluation, and the effects they induce differ from those of the inhibitors of the CTLA4 and PD-1/PD-L1 pathway.

For example, agonist mAbs targeting CD137 increase the activity of activated NK or other cells of the innate and adaptive immune system, without inducing clonal expansion, as checkpoint inhibitors do.

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IDO inhibitors unbind many T-cell effectors from IDO control, but a strong increase in tumor infiltrating lymphocytes is unlikely.

In these cases, the appearance of a pseudoprogression is doubtful and delaying the change of therapy may endanger the patients.

In conclusion, irRC represent components of a valid tool in clinical trials, but their use in clinical practice, in their present form, seems less convincing.

Moreover, new immunotherapies with different targets act in ways other than checkpoint inhibitors do. In these cases, irRC may need further validation.

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

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