Alternative biomarkers for immunotherapy

TURID HELLEVIK

E-mail: turid.hellevik@unn.no
Turid Hellevik, dr.scient. radiation physicist and senior researcher in translational radiation oncology in the Department of Oncology at the University Hospital of North Norway.
The author has completed the ICMJE form and declares the following conflicts of interest: She has received research funding from the Norwegian Cancer Society for 2018. One of the work packages in the approved research project concerns development and testing of tracers based on the immuno-PET concept.

IÑIGO MARTINEZ-ZUBIAURRE

Iñigo Martinez-Zubiaurre, professor of cell biology who conducts experimental research in translational radiation oncology. He is head of the Molecular Inflammation research group in the Department of Clinical Medicine, University of Tromsø – The Arctic University of Norway.
The author has completed the ICMJE form and declares the following conflicts of interest: He has received research funding from the Norwegian Cancer Society for 2018. One of the work packages in the approved research project concerns development and testing of tracers based on the immuno-PET concept.

The increasing use of immunotherapy in cases of metastatic cancer has revealed an urgent need for predictive biomarkers. Here, molecular imaging is presented as a unique candidate for the development of robust biomarkers for cancer immunotherapy.

Immunotherapy, in the form of checkpoint inhibitors, offers new hope of additional years of life for cancer patients with metastasis, and has in many ways revolutionised cancer therapy (1). However, despite the measurable and increasing clinical success of cancer-related immunotherapy, it is still a fact that only a small proportion of patients respond positively to this form of treatment. Besides the need to increase response rates, efforts to establish immunotherapy in the clinic face two additional challenges. First, novel immunotherapy drugs are expensive, and second, treatment can be associated with some serious side effects. Hence, there is a pressing need for solid biomarkers, so that patients who may benefit from immunotherapy can be selected prior to treatment initiation (2). Here, we underscore the concept of 'molecular PET imaging' as a tool to address some of the clinical challenges associated with cancer immunotherapy.

PET imaging versus needle biopsy

The current practice of selecting patients based on needle biopsies from tumour tissue has some clear limitations and drawbacks. These limitations are primarily related to the fact that it is difficult to ensure that a tiny needle biopsy is representative for the entire tumour,

as most solid tumours consist of a highly heterogeneous population of cells (3). In addition, there are inaccuracies related to manual scoring and to the choice of threshold levels for marker expression. Furthermore, a needle biopsy is an invasive procedure, typically performed before treatment initiation, and is not suitable for response evaluations.

Both the applicability and the amount of information that can be obtained from PET imaging are in marked contrast to what can be achieved by a single needle biopsy

Imaging with positron emission tomography (PET) has recently been adopted by the Norwegian health authorities, and now constitutes an important diagnostic tool for assessing the extent of disease in cancer patients (4). The visualisation of cancerous tissues begins with the careful selection of a biological molecule, followed by its labelling with a radioactive isotope. After injection into the circulation and uptake by tissues, the resulting radiotracer will light up on the images emerging from a PET scan. Tissue-uptake of a radioactive compound reflects the physiological or pathological distribution of specific molecules. The benefits of PET imaging are many: Visual and quantitative information is obtained on a target molecule, not only throughout the entire tumour tissue, but across large areas of the body – thereby uncovering the existence of both primary tumours and remote metastases. The fact that the procedure is non-invasive and can be used repeatedly, offers the possibility to detect dynamic changes and to assess therapeutic responses. Hence, both the applicability and the amount of information that can be obtained from PET imaging are in marked contrast to what can be achieved by a single needle biopsy.

Pseudoprogression of tumours

Immunotherapy has also generated a need for new tools that can define treatment responses. One reason for this is that immunotherapy can induce (transient) increases in tumour size, due to recruitment of different immune cells. This 'pseudoprogression' is often a positive indicator of treatment response, but is difficult to distinguish from genuine disease progression using standard imaging modalities such as CT, MRI and glucose-based PET (5). These clinical realities have triggered intense international research efforts to resolve the problems associated with cancer immunotherapy. As a result, much of the research within the field of molecular imaging is aimed at distinguishing the tumour versus immune cell content of solid tumours.

Development of new radiotracers

Specific molecular imaging by so-called immuno-PET technology is a relatively new concept, and comprises visualisation through uptake of antibody-based tracers (6). Immuno-PET imaging introduces the possibility of quantifying expression of specific target molecules. In the context of cancer immunotherapy, imaging a tumour's immune status may be more relevant than imaging tumour cells or the entire tumour mass, typically achieved through PET scanning by non-specific uptake of glucose. For immunotherapy purposes, relevant imaging targets are subtypes of immunological T-cells (such as CD8+ and T-regs), and receptors for checkpoint inhibitors, such as PD-1, PD-L1 and CTLA-4 (7).

In conclusion, antibody-based tracers and associated immuno-PET imaging provide the opportunity of visualising – rapidly, quantitatively and without prior fasting – the immunological status of human tumours. Considering immunotherapy as a fourth modality within professional cancer care, immuno-PET technology would appear to be a highly promising complementary tool for patient selection and response evaluation. This should be good news for cancer patients and for hospitals.

REFERENCES:

1. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science 2013; 342: 1432–3.

[PubMed][CrossRef]

2. Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. Nat Rev Cancer 2019; 19: 133–50. [PubMed][CrossRef]

3. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100: 57–70. [PubMed][CrossRef]

4. Pantel AR, Mankoff DA. Molecular imaging to guide systemic cancer therapy: Illustrative examples of PET imaging cancer biomarkers. Cancer Lett 2017; 387: 25–31. [PubMed][CrossRef]

5. Carter BW, Bhosale PR, Yang WT. Immunotherapy and the role of imaging. Cancer 2018; 124: 2906–22. [PubMed][CrossRef]

6. Marciscano AE, Thorek DLJ. Role of noninvasive molecular imaging in determining response. Adv Radiat Oncol 2018; 3: 534–47. [PubMed][CrossRef]

7. Chatterjee S, Lesniak WG, Nimmagadda S. Noninvasive imaging of immune checkpoint ligand pd-l1 in tumors and metastases for guiding immunotherapy. Mol Imaging 2017; 16.. [PubMed][CrossRef]