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Tumour-agnostic drugs and future cancer treatment

KRONIKK

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In November 2018, a tumour-agnostic drug was approved in the United States for use against cancer. The term 'tumour-agnostic' is not immediately intuitive, and many are probably unaware of the approval of the drug larotrectinib. But tumour-agnostic drugs may be of great importance for future cancer treatment.

Illustration: Sylvia Stølan

Following the introduction of imatinib almost 20 years ago, we have become accustomed to the term 'targeted cancer treatment'. It refers to treatment that targets the molecular changes in the cancer cells that drive tumour development. An example of a molecule that has been modified in this way, often referred to as an oncoprotein, is the fusion protein BCR-ABL, which is a disease driver in the majority of patients with chronic myeloid leukaemia and in many of those with acute lymphoblastic leukaemia. It is not unusual for a particular oncoprotein to be found in several different cancers, and a targeted drug may therefore be effective against tumours with very different histological classifications. For example, the tyrosine kinase inhibitor dabrafenib is approved for the treatment of two

cancers as diverse as melanoma and non-small cell lung cancer, provided that the tumour has a specific mutation in the *BRAF* gene.

However, none of the targeted cancer drugs approved for use in Norway have indications that are detached from traditional histological classification. These indications are based on the organ or tissue from which the tumour originated. It is this link between histology and therapy that has now been broken by the decision of the U.S. Food and Drug Administration (FDA) in November to approve the drug larotrectinib with a *tumour-agnostic* indication (1). 'Tumour-agnostic' is a composite of words with Latin and Greek origins respectively, and means 'without knowledge of the tumour'. Larotrectinib was approved for the treatment of adults and children with solid tumours with a tropomyosin receptor kinase (*NTRK*) gene fusion. There is also a requirement for the tumour to have metastasised or for the patient to have no other treatment options available, but there is no link to histological classification. Agnostic, in this context, means that knowledge of the histological classification of the tumour has no bearing on the choice of drug.

First purely tumour-agnostic drug

Larotrectinib is the first drug with an exclusively tumour-agnostic indication. However, as early as May 2017, the immunotherapeutic antibody pembrolizumab, which targets the immunoinhibitory receptor PD1, was approved by the US pharmaceutical authorities with a tumour-agnostic indication (2). The approval applied to the treatment of metastatic solid tumours with microsatellite instability. The indication was thus based on a specific biomarker, but not on the histological tumour type. Unlike larotrectinib, pembrolizumab was already approved for the treatment of melanoma and certain other tumour types when it additionally received a tumour-agnostic indication.

Larotrectinib can only be given to patients with tumours in which the oncogene *NTRK* is detected as a biomarker. This gene exists as three variants, *NTRK* 1, 2 and 3, which encode tropomyosin receptor kinase (TRK) A, B and C, respectively (3). TRK molecules are found in the cell membrane and are receptors for the neurotrophin class of cytokines. Each of the receptors has its own preferred ligands, but there is also a degree of promiscuity. This means that neurotrophins present at high concentrations can also activate receptors other than their own. The receptors are best studied in nervous tissue where they are expressed by neurons and are important for normal development of both the central and peripheral nervous systems. The receptors are also expressed in a variety of cells in other tissues of the body such as the bones, lungs, pancreas and immune system (4). The binding of a neurotrophin to a TRK receptor activates the receptor and triggers a signalling cascade inside the cell via several different signalling pathways, for example, the mitogen-activated protein kinase pathway. Depending on the cell type, the signal initiates a cellular programme for differentiation, cell division or protection against apoptosis (4).

Oncogenes and oncoproteins

The first case of an *NTRK* gene acting as an oncogene was discovered back in 1982, the same year that patients with chronic myeloid leukaemia were shown to have a fusion between the *Bcr* and *Abl* genes (5). But it was only when the sequencing of DNA and RNA from cancerous tumours began on a large scale that the extent of gene fusions involving *NTRK* genes became apparent. In contrast to the *Ab1* gene, which has *Bcr* as its preferred fusion partner, *NTRK* genes are converted to oncogenes by a whole range of different partner genes. About 50 different proteins have been identified as partners, mainly proteins with a dimerisation domain, which replaces the extracellular portion of the TRK receptor after fusion (3). The dimerisation domains cause pairs of fusion proteins to join together, resulting in activation of the intracellular domain of the receptor for signal transduction in the absence of bound neurotrophin.

Another characteristic of *NTRK* oncogenes is that they occur in a variety of cancers (4). These

include relatively common cancers such as lung cancer, colorectal cancer and glioblastoma, although they are found in only 1–3 % of these patients. They are even less frequent in patients with melanoma or squamous cell carcinoma of the head and neck. By contrast, the incidence of *NTRK* oncogenes in the rare cancers congenital fibrosarcoma and secretory breast carcinoma is almost 100 % (4).

Larotrectinib, and the investigational drug entrectinib, are small-molecule drugs that block the signal from TRK oncoproteins. The approval of larotrectinib by the U.S. pharmaceutical authorities was based on an analysis of three phase 1 and 2 studies in 55 children and adults with 17 different *NTRK* fusion-positive cancers (6). The results of the studies were published in the *New England Journal of Medicine* in February 2018 and showed a long-term clinical response in 75–80 % of patients, with no grade 4 or 5 adverse events considered to be drug-related. The most frequent adverse event was AST or ALT elevation, which was detected in approximately 40 % of patients (6).

Identifying patients

The relatively few patients who can benefit from larotrectinib must thus be identified from among a large group of patients with a variety of different cancers. In Bayer's application to the Norwegian 'Ordering Forum' to have larotrectinib considered for use by the specialist health service, they estimate that the applicable patient group in Norway will comprise about 90 persons per year (7). At the same time, they acknowledge that no more than about half of these will be identified.

Testing for *NTRK*-fusion genes or TRK-fusion proteins can be performed in various ways. Nucleic acid sequencing, fluorescence in situ hybridisation (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) can all detect fusion genes, while immunohistochemistry can detect the proteins. There are methodological challenges associated with all of these tests, in part because of the many different fusion partners. There is also the question of how low the incidence of these mutations must be in a particular type of cancer, for it to be acceptable not to test for these oncogenes. Similar issues have arisen with other biomarkers that influence choice of therapies. However, the issue is particularly crucial here because the volume of samples is likely to be very high, which means that offering to test patient populations with a low mutation incidence would lead to a high threshold cost for each additional patient identified. At the same time, there is reason to believe that similar challenges will arise following the development of new drugs targeting other low frequency oncoproteins. Tests based on high-throughput sequencing that can detect many different oncogenes simultaneously, including *NTRK*-fusion genes, will probably enter general usage shortly. Such tests may be less expensive than a battery of tests for single oncogenes and will provide an oncogenic profile for an individual tumour. The benefits of such a profile will, of course, depend on how informative the profile is for prognosis and how influential it becomes for choice of therapy.

A new direction for oncology?

The introduction of tumour-agnostic drugs gives cause for reflection on the classification of tumours. Will organ and tissue-based classification gradually be superseded by a preliminary molecular sorting of cancerous tumours? Will we eventually refer to, for example, 'a TRK tumour with colon localisation'? Certainly, oncology cannot be tumour-agnostic in the most basic sense of the word. It is an oxymoron to refer to new knowledge as a lack of knowledge, but perhaps our old knowledge may be about to become less relevant.

REFERENCES:

1. U.S. Food and Drug Administration. FDA approves larotrectinib for solid tumors with NTRK gene fusions. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm626720.htm (11.1.2019).

2. U.S. Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication:
https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm (11.1.2019).

3. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol 2018; 15: 731–47. [PubMed][CrossRef]

4. Vaishnavi A, Le AT, Doebele RC. TRKing down an old oncogene in a new era of targeted therapy. Cancer Discov 2015; 5: 25–34. [PubMed][CrossRef]

5. Pulciani S, Santos E, Lauver AV et al. Oncogenes in solid human tumours. Nature 1982; 300: 539–42. [PubMed][CrossRef]

6. Drilon A, Laetsch TW, Kummar S et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018; 378: 731–9. [PubMed][CrossRef]

7. Vitrakvi (larotrectinib) i NTRK fusjonsgen positiv kreft. Forslag om nasjonal metodevurdering. Oslo: Bayer AS, 2017.
https://nyemetoder.no/Documents/Forslag/ID2018_114%20larotrectinib%20(Vitrakvi)%20til%20behandling%20av%20NTRK%20fusjonsgenpositiv%20kreft%20(Forslag).pdf (11.1.2019).

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