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Precision cancer medicine – still expedient for the few

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Cancer genome sequencing with the aid of next-generation sequencing is now being introduced as part of routine diagnostics. It allows for off-label treatment of patients with advanced cancer. Unfortunately, this strategy is often to no avail.

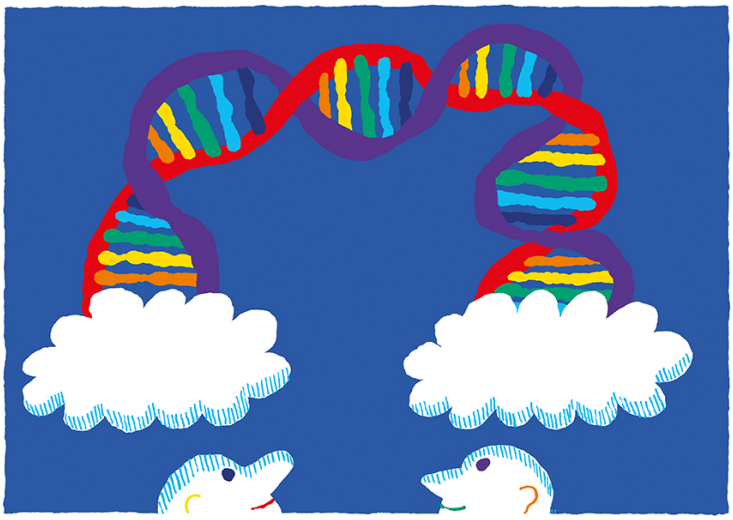

Illustration: Espen Friberg

The principle of large-scale DNA sequencing with high-capacity technology was first described in 2005 and was soon given the name *Next Generation Sequencing* (NGS) (1). The method entails the simultaneous sequencing of many hundreds of genes or even larger genome segments (wide analysis) many hundred or several thousand times (deep analysis). It is possible to detect any mutations in specific individual genes among a large number of 'uninteresting' genes.

In the 15 years that have passed since this breakthrough, cancer researchers worldwide have used NGS technology to describe the genetic constitution of different types of cancer.

Major institutions internationally have also introduced NGS diagnostics for cancer tissue in

order to stratify individual patients with advanced cancer for off-label treatment with drugs that are adapted to the biological effect of the presumed driver mutation in the tumour. The principle is that a drug matched to the driver mutation in one type of cancer for which the therapeutic indication has been established on the basis of large-scale efficacy trials, can also be useful when the same driver mutation is found in another type of cancer, for which there is no indication for the drug.

Now in 2020, accumulated data from almost 20 000 patients show that 5 %, or even fewer, have had proven therapeutic benefit from such treatment given off-label (2, 3). As oncologists we have a duty to provide dispassionate information on the possible benefits of precision cancer medicine to our patients with advanced cancer, as well as in the health policy discourse.

Diagnostic prerequisite

For many years, pathologists have performed a small selection of DNA analyses in the field of cancer diagnostics, but analysis of a large assortment and many types of genetic mutations is now called for. For example, an increasing number of molecular tumour alterations have a predictive value for the choice of standard therapy. Many experimental clinical trials comprise particular molecular subgroups within a single type of cancer, or across multiple cancer types. It is therefore high time that NGS technology is introduced routinely to replace single gene analyses. For desperate patients, this would also replace their pursuit of NGS diagnostics offered by private providers (who set the price of the analysis far above the real cost of the product, the quality of which is unknown to the patient's oncologist) with quality-assured diagnostics that also build this competence within the public health service.

Therapeutic prerequisite

For a long time, we have treated cancer with drugs that are adapted for the biological consequences of specific tumour mutations when convincing findings from efficacy studies are available. A well-known study from as early as 2001 showed that for previously untreated patients with metastatic breast cancer with amplification of the *ERBB2* gene (then known as the *HER2* gene) who received the targeted drug trastuzumab in combination with chemotherapy, the duration of the therapeutic effect was almost twice that for patients who were randomised to chemotherapy alone (4). Among more recent studies, crizotinib that targets the biological effect of the *ALK* fusion gene doubled the duration of the therapeutic effect compared to standard chemotherapy for this subgroup of patients with advanced non-small cell lung cancer (5). Now, in 2020, we can point to many similar examples. However, *ERBB2* amplification, *ALK* fusion and many other specific gene mutations also occur as very rare findings in a number of cancer types, and it may be appropriate to regard these as driver mutations that could serve as therapeutic targets.

Precision cancer medicine and therapeutic effect

The term 'precision medicine' is frequently used in a narrow sense in connection with cancer – the idea of providing a drug targeted to an identified tumour mutation, but off-label, to patients with advanced disease after all other systemic tumour-directed treatment has failed. Precision cancer medicine in this sense was launched at the ASCO conference (the world's largest clinical oncology conference) in the spring of 2011 when The University of Texas MD Anderson Cancer Center presented its ongoing long-standing programme in the field of biomarker-driven experimental cancer therapy, published the following year (6).

During the subsequent decade, many extensive initiatives of the same type and generally based on NGS diagnostics were undertaken at large oncology institutions in a number of countries (7–16). When correctly interpreted, the outcome data are disappointing.

The correct outcome measure, the objective response rate, must have the number of patients who undergo NGS analysis as the denominator and the number of patients who achieve an objective therapeutic effect (partial or complete response, determined radiologically) as the numerator. However, reports from clinical trials more or less intentionally emphasise the number of patients who end up starting treatment, not all those who are tested, as the denominator (which is therefore artificially low). Moreover, the number of patients who have radiologically defined stable disease, in addition to those with an objective response, is reported in the numerator (which is thus artificially high). The outcome data are thereby inflated.

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In simple terms, stable disease in cases of metastatic cancer means that the patient's burden of disease over a predefined treatment period increases by less than 20 % or is reduced by less than 30 %, which are rather arbitrarily chosen radiological target figures. The definition 'stable disease' in itself gives no indication of the extent of the metastatic burden of disease, which is often substantial in end-stage cancer.

A telling example of why stable disease cannot be deemed a treatment response can be seen in patients with widespread liver metastasis which results in hepatic capsule stretch. When the therapeutic outcome in such a patient is scored as stable disease, the patient has thus experienced no change in pain level from the hepatic capsule stretch, as well as adverse effects from the treatment, in the final stage of life – therefore no therapeutic benefit! This poses the rhetorical question: Is it right to report such an outcome as a success for experimental precision cancer medicine? For information, we generally give these patients a daily dose of prednisolone, a simple and inexpensive treatment of the symptoms in question.

Inflated and real outcome data

A number of large-scale trials in precision cancer medicine in end-stage cancer have been published in the last five years (7–11). In several of these, other molecular methods were used in addition to NGS technology, in the hope of revealing and targeting different biological signalling pathways in the tumour tissue than those indicated by the sequencing data alone. The studies have reported an objective response in 11–36 % of those who received treatment, with progression-free survival of a few months. However, these figures include only 2–4 % of all included patients who had undergone tumour analysis. The French SHIVA trial is the only one to date that has randomised patients in whom a tumour mutation for which a drug exists had been identified, to receive the drug in question or standard therapy instead, and progression-free survival ended up the same in the two patient groups (12).

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A way of 'circumventing' the need to account for the fact that in many patients a treatment goal is not identified, is to define patient populations that fulfil the molecular criteria for treatment in advance or during the trial, and then report the outcome only for these patients. This is in essence a sensible study design, but it is also important to be aware that the real number in the denominator of the response measure – how many have been tested in order to find those patients who qualify – is unknown. In the NCI-MATCH study from the United States, the first objective response rates reported are only 5–8 % (13, 14) even with these selection criteria. In the DRUP study from the Netherlands, the corresponding figure is 15 % (15). This type of study design, however, has little value for evaluating the benefit of precision medicine for the total patient population with end-stage cancer.

Lessons from the MetAction trial

On returning home from the ASCO 2011 conference, we were motivated to apply for funding from the Research Council of Norway. We were delighted when in the spring of 2012 we received a grant that was able to fund the MetAction trial, Norway's first clinical trial of precision cancer medicine. After a long period of planning, we included 24 study patients from May 2014 to August 2015 in order to test and evaluate all the necessary diagnostic elements (16). The most important of these proved to be competence building among all the experts involved.

In the next part of the study, with the inclusion of 26 patients from March 2016 to March 2017, ten of these patients received treatment based on NGS data from metastatic tumour tissue (3). Of these, two colorectal cancer patients achieved a partial therapeutic response with a duration of 10–17 weeks before new disease progression. A further two colorectal cancer patients had tumour mutations that argued for immunotherapy, whereof one mutation was extremely rare (17). Both achieved complete response (status as of 2020)! However, with the exception of these two patients, survival from the time of inclusion in the trial was identical for the two patient groups who received and did not receive treatment based on NGS findings. In three patients with gastrointestinal cancer we identified *ALK* or *ROS1* fusion as the assumed driver mutation, and in these cases crizotinib gives convincing therapeutic outcomes in advanced non-small cell lung cancer (5, 18). However, the MetAction patients had no therapeutic benefit from crizotinib, which runs counter to the concept of biologically targeted drugs used off-label (3).

Conclusion

In the MetAction trial we took account of tumour mutations that indicated resistance as well as response to therapy. Findings of the first-mentioned mutation type have not been clearly reported in the large-scale international studies. Despite the conservative interpretation of NGS data in our study, only two of 26 patients experienced a long-term treatment effect of precision cancer medicine, both patients on immunotherapy. Precision medicine for advanced cancer should certainly have its place in the overall treatment pathway because it benefits a certain few patients—and we must identify them! But we must refrain from giving false hope to the majority.

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