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Metastatic cancer

Metatastic cancer is one of the greatest challenges for the pharmaceutical industry. Are healthcare companies rising to meet it?

What is metastatic cancer?

Metastasis is the spread of cancer cells to new areas of the body, often by way of the lymph system or bloodstream.

If the cancer has moved into nearby tissue or lymph nodes, it has spread but not fully metastasised. Only when the cancer has spread far from its original site does it become metastatic. Metastatic cancer is usually terminal.

Even after metastases, the cancer is named after the part of the body in which it originated. So, a patient with breast cancer that has infected lung tissue has breast cancer with lung metastasis.

How does metastatic cancer progress in the body?

As metastatic cancer spreads through the body, it goes through the stages of a 'metastatic cascade' and a number of processes take place. First, cells in the primary tumour gain metastatic potential and begin to migrate into local tissue.

Eventually, the cancer cells enter the blood or lymph and circulate through a process known as epithelial-mesenchymal transition (EMT), turning into circulating tumour cells (CTCs).

Many CTCs die or are destroyed as a result of the inhospitable environment of the human body, largely due to its immune response. However, some can survive to permeate into tissue. If the CTCs find a suitable environment, they will take root.

This is the 'seed and soil' concept first described by Stephen Paget. Seeds naturally favour different soils, for example the most fertile field for most prostate cancer is bone.

The seeded cells can then lie dormant, sometimes for years in tissues like bone, where they can remain in 'disseminated tumour cell niches'. In the end-stage of the metastatic cascade, these 'seeds' will begin to grow and colonise tissue.

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'A major focus in oncology currently is on shrinking established tumours in advanced stages of cancer, usually leading to a small survival benefit. An obvious strategy is to try to prevent or halt the metastatic process before patients reach such an advanced stage of disease. Such therapies could have significant potential across a variety of metastatic cancers. However, this area is more complex for drug development, partly due to a lack of understanding of the metastatic process.' Jonas Peciulis, healthcare analyst.

Why is metastatic cancer so difficult to treat?

Therapies for metastatic cancer suffer from hurdles not often shared by earlier-stage variants. For example, the targets of metastatic therapies are not very 'druggable', in that they often lack the enzymatically active sites onto which small drug molecules and antibodies can naturally bind. This makes drug delivery a challenge.

Metastatic cells also use multiple pathways in the various stages of the metastatic cascade, so targeting a single pathway is not sufficient to prevent the cancer spreading. Clinical trials in anti-metastatic drugs have also been hindered by difficult endpoints focused on prevention.

That has changed as the FDA and EMA now allow metastasis-free survival as an endpoint for clinical trials. This endpoint has already been used successfully for the approval of the new prostate cancer therapies, apalutamide and enzalutamide, in high-risk, non-metastatic, castrate-resistant prostate cancer. The new endpoints should also shorten the duration and lower the cost of trials in anti-metastasis drugs.

That said, metastatic-focused clinical trials still suffer from long trial periods, due to the long progression of the disease, especially with slowly progressing variants like prostate cancer.

Given the difficulties of developing metastatic cancer drugs, why develop them?

There is a belief that, given the difficult nature of metastatic cancer, efforts are better spent on the early detection and treatment of cancers and preventative medicine. Unfortunately, a large proportion of patients diagnosed with cancer already have metastases.

Limiting or delaying further metastasis might be achievable, while treating established tumours with tumour-shrinking therapies. However, even if a patient is 'cured' of early-stage cancer, successfully removing or destroying the primary tumour, they can still relapse as cancer cells are constantly entering circulation from the primary tumour throughout its existence.

Therefore, even if there are no diagnosed metastases, several stages of the metastatic cascade might have taken place in a patient. With this in mind, it is worthwhile considering specifically targeting the metastatic process in cancer drug R&D.

Which companies are developing anti-metastatic drugs?

Despite its importance in cancer progression, there has been a general lack of enthusiasm from the pharmaceutical industry in relation to the metastatic cascade. The main reason for this is the difficulty of successfully bringing such a drug to market.

There are, however, a few notable drugs that have targeted stages in the metastatic cascade. Roche's bevacizumab (Avastin), which targets blood vessels around cancer growths, is the most commercially successful, but its main use is in primary tumours.

Amgen's Denosumab, a RANKL inhibitor that stops the overproduction of osteoclasts associated with bone cancers, has been one of the most successful metastasis inhibitors so far. However, its scope does not extend much further than bone disease, including osteoporosis.

RhoVac is developing a new immunotherapy aimed at activating T-cells against the protein RhoC. The company has one clinical programme in prostate cancer and is currently raising funds for a Phase II study.