PERSPECTIVE

The right trials

The system for clinical trials must be redesigned if there is to be a decline in breast cancer metastasis, argues **Patricia S. Steeg**.

Most people with breast cancer die as a result of tumour metastases, either directly or indirectly. Surgery, the first-line treatment for breast cancer, eliminates most primary tumours in conjunction with radiotherapy. But metastatic disease, in which the primary tumour spreads and colonizes other tissues, is largely incurable.

Chemotherapy is often given after surgery to prevent recurrence of the disease. Most of the approved systemic therapies for breast cancer — including cytotoxic chemotherapeutics (which kill cells), HER2 inhibitors and oestrogen-pathway antagonists — inhibit the growth of primary tumours. They can also shrink metastatic tumours. Some can even prolong patient survival. But we need to do better.

FROM MACRO TO MICRO

Cancer therapeutics inhibit tumour growth, but there is more to cancer than growth. To reduce the incidence of metastatic disease, drug development should target the metastatic process itself. Metastases are distinct from the primary tumour, in terms of both the tumour cells themselves, which have different mutations and gene-expression profiles, and the surrounding microenvironment. As such, they provide opportunities for developing new lead compounds.

Metastasis-preventive compounds could block any number of steps in the metastatic process: invasion (or escape) of cells from the primary tumour into the bloodstream, survival in the circulation, avoidance of the immune system, arrest and egress from the circulation (when, for example, circulating tumour cells get stuck in a capillary and escape into the tissue through the blood-vessel wall), or successful colonization of a distant organ. Because about one-third of patients with breast cancer have 'positive' lymph nodes (those containing tumour cells) at the time of surgery, indicating that the initial invasion process is already complete, drugs that target metastatic colonization may prove to be the most efficacious.

Researchers have developed and validated compounds that can inhibit a wide range of metastasis-related pathways in animals. Examples are inhibitors of intracellular signalling molecules (including SRC and FAK), compounds that block cell adhesion to the extracellular matrix, and inhibitors of soluble chemokines (cell attractants) or other cytokines[1–4]. In most of these animal studies, tumour cells were injected into the animal to form a primary tumour or injected directly into the circulation (to mimic escaped circulating tumour cells), and the compound was then promptly and continuously administered. The result was that the tumour cells never formed a distant lesion — in other words, the compound prevented metastasis formation. By contrast, when tested on metastases that had already formed, few of these compounds shrank the tumours. This makes intuitive sense as established metastases contain more tumour cells and have a poorly organized blood supply, both of which are impediments to drug delivery and efficacy. Preventing metastasis development has the potentially more attainable goal of targeting a small number of tumour cells as they are beginning to colonize the body.

SYSTEM FAILURE

There is a huge barrier to developing agents that prevent breast cancer metastasis. If such agents were tested in the current clinical-trial system, many would fail. Simply put, clinical trials are not designed to test metastasis-preventive compounds.

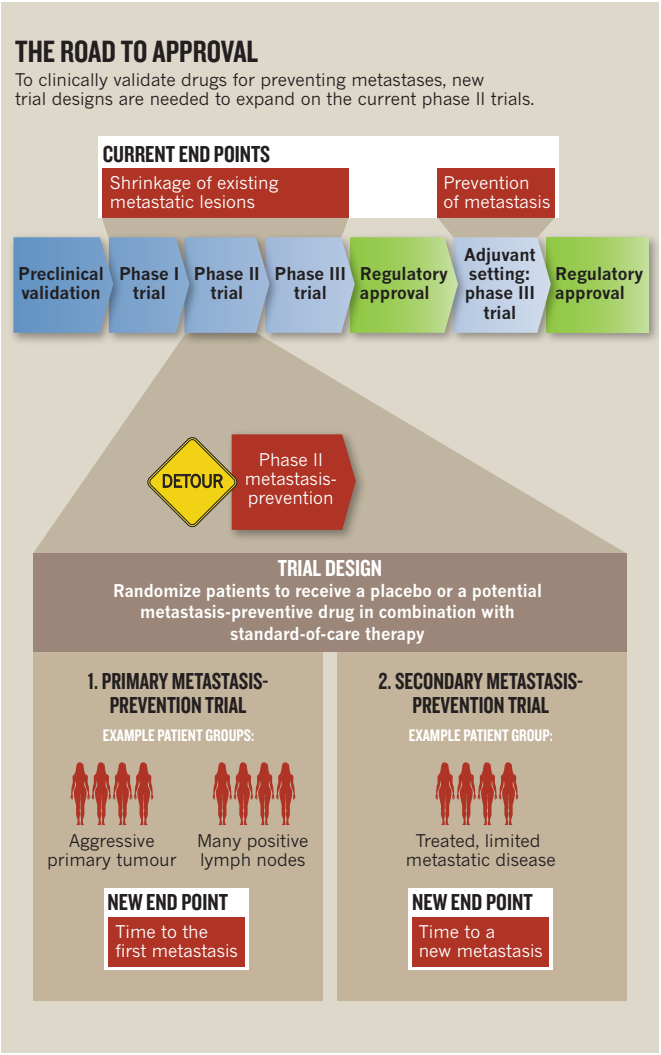
Today, a potential anticancer drug is first tested in phase I (safety and toxicity) trials in the hardest-to-treat patients: those with metastatic cancer that is resistant to treatment. It must then be shown to have efficacy (to shrink established metastases) in phase II trials, and to provide a benefit to patients over the current standard of care in phase III (validation) trials, before gaining regulatory approval. Only then might additional trials be conducted to determine whether the drug can prevent metastases — when given as an adjuvant in combination with the standard treatment regimen, in a healthier breast cancer population. Such trials are rare, however, because they require large patient numbers and are expensive. Only the oestrogen-receptor antagonist tamoxifen, the HER2 inhibitor trastuzumab (Herceptin) and cytotoxic drugs, all of which can shrink established tumours, have been validated in adjuvant trials.

THE ONCOLOGY COMMUNITY AS A WHOLE NEEDS TO COMMIT TO DOING SOMETHING DIFFERENT.

Inhibitors of metastasis are not intended to be cytotoxic or necessarily to synergize with traditional chemotherapeutics. Consequently, any such compounds tested in phase II trials might do little to shrink established tumours and would eventually be shelved. The drug company loses the money invested in development; the scientists who worked on these compounds lose a potentially valid clinical lead compound; and the patients continue to lose their lives.

A DIVERGENT APPROACH

A new clinical-trial design is needed. This design must incorporate preclinical and clinical data in a rational manner and measure end points that are appropriate for metastasis prevention. I propose a detour from the linear model of clinical development either before or just after phase II trials (see 'The road to approval'). I recommend that randomized phase II trials be carried out for metastasis prevention. These trials would test compounds that have been shown to prevent metastasis in animal studies, that have few side effects in phase I trials and that work safely with existing drug combinations in the clinic. The trials would enrol selected patients — those who are at high risk of recurrence or who already have limited metastatic disease — who would be randomized to receive either the candidate preventive agent or a placebo. The most important end point would be the time until a new metastasis occurs — not shrinkage of an existing tumour.



In this scheme, there are two potential types of metastasis-prevention trial. In primary prevention trials, the end point would be the time to development of the first metastasis. To expedite the testing, such trials should enrol patients who do not have metastases but who are at high risk of disease progression. An example of suitable participants are patients who have undergone therapy to shrink their aggressive primary tumours before surgery but whose tumours failed to respond. Patients who were found to have a large number of positive lymph nodes at surgery could also be candidates. In secondary prevention trials, the patients would have limited metastatic disease. The end point would be the time to development of a new metastasis. Potential study populations include patients with cancer that has recurred in the chest wall (who are at high risk of further metastases), patients whose metastases were successfully treated (but who might still be harbouring micrometastases) or patients who were treated with stereotactic radiotherapy (radiation delivered by several precisely targeted beams) for at least one brain metastasis (another high-risk group for further metastases).

Clearly, the design of metastasis-prevention trials must allow patients to continue receiving their current treatments. There are two potential approaches. The first is the 'dealer's choice' option. Each patient is offered several potential backbone therapeutics that can be safely used in combination; the patient and oncologist can select the most appropriate combination. This design may require a larger trial size because of the number of standard drugs included, but it will be appropriate to patients' needs. If a patient has an existing metastasis and it grows, she could continue in the secondary prevention trial by switching to another chemotherapy option from the dealer's choice list. The second approach would limit the number of systemic therapies needed, by conducting these studies in separate subgroups of breast cancer patients: for example, HER2 positive, oestrogen-receptor positive, and triple negative (which does not express any receptors). This approach would reduce the number of choices available and hence the complexity and overall size of the trial.

THE END POINT

There is no denying that such a trial design would be a complex undertaking. After an initial signal of success, additional trials would be needed to settle issues such as the maximum tolerated dose versus the biologically effective dose, and the optimum sequence and duration of therapy. Moreover, successful prevention of metastasis is likely to require a combination of metastasis-preventive drugs, given the number of pathways involved in this process and the potential for tumour cells to mutate.

A positive result in these phase II preventive trials would mean that the drug could be approved for use in patients with limited metastatic disease, to halt further progression. These results could be expanded with further trials to determine a more successful cocktail of metastasis preventives. Next would come a full adjuvant trial, in which healthier breast cancer patients with large primary tumours or any positive lymph nodes would be randomized to receive the standard of care with or without the metastasis-preventive drug.

FORGING AHEAD

Why haven't such trial designs been tried? The closest example is the November 2010 approval by the US Food and Drug Administration (FDA) of denosumab for the prevention of 'skeletal-related events' (a hybrid term that includes side effects from an existing metastasis or new metastases) in patients with breast or prostate cancer that has spread to the bones. Denosumab inhibits the protein RANKL, which is a component of a vicious cycle that involves the stimulation of bone-destroying osteoclasts and further stimulation of tumour cells. The drug had already received approval under a different trade name for the treatment of postmenopausal osteoporosis.

Preclinical studies showed that inhibiting RANKL prevented metastasis to the bones. In clinical trials, men with castration-resistant (not responsive to antihormone treatment), non-metastatic prostate cancer remained metastasis free for significantly longer when treated with denosumab[5]. Denosumab was also tested in patients with breast cancer that had metastasized to the bone and was found to delay the time to a new skeletal-related event. Aspects of these trials are comparable to a secondary metastasis-prevention trial.

These examples are painfully few. Metastasis prevention needs additional input and guidance. The FDA must address the subject of metastasis-preventive compounds so that clinical trialists and statisticians can crunch the numbers and appropriately design prevention trials. The oncology community as a whole needs to commit to doing something different. This concept clearly applies to cancers other than breast cancer, potentially affecting millions of patients who fear the recurrence of a disease they hoped they had beaten.

Let's start this process — now. ■

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