Targeting metabolic pathways: why are we missing a trick in cancer treatment?

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BIOLOGICAL AND TARGETED THERAPIES, IMMUNOTHERAPY

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A new route to effective cancer treatment is emerging from research showing impressive results from drug cocktails of immunotherapy and metabolic medicines alongside conventional chemotherapy.

The evidence from a growing number of studies suggests that using this approach to interfere with the abnormal metabolic pathways used by cancer cells could dramatically boost the efficacy of the current generation of precisely targeted and hugely expensive first-line cancer treatments.

The agents that could have this additional effect include statins, metformin, doxycycline and mebendazole – not drugs normally associated with an oncologist's armory, but ones that appear to work on metabolic pathways that are common to most cancerous growths.

This drug combination has been demonstrated to interfere simultaneously with a number of proteins or signaling pathways. The effect is to kill cancer cells, prevent their multiplication or reprogram them to behave like healthy cells.

Used together, the drugs could change the outlook for the 150,000 cancer patients in Britain alone, who every year are told there is nothing more that can be done to halt progress of their disease. They could also save vast sums spent on chemotherapy and immunotherapy treatments that can prove ineffective for the majority of patients offered them.

In the past few weeks alone, studies from the US have shown that an antibacterial treatment can block growth of most types of cancer tumor in preclinical models [1]; that male prostate cancer patients given statins survive longer without tumor regrowth [2], and that women with cancer could be up to 50% less likely to die if they receive statins [3].

An earlier meta-analysis of metformin involving 1.5 million individuals also demonstrated that metformin users enjoyed not only a substantial reduction in the risk of getting cancer, but also a significant reduction in the risk of dying once they had developed the disease [4].

There are signs that other drugs could confer the same benefits, but it is the four agents mentioned above that have so far drawn the most interest.

Their modes of action are well studied, they have overlapping effects and there is no current evidence suggesting that they may cause harm.

Metformin

Numerous trials have shown that metformin, routinely used to treat diabetes, also inhibits the development of cancer cells. The precise mechanisms are not understood however, and the drug may have different effects in different types of cancer.

There is some evidence that metformin blocks a malfunctioning pathway for Stat3, a master protein that controls the production of other molecules vital to cell signaling in cancer cells [5].

Metformin has also been shown to alter the effect of malfunctioning Bcl-2 and Bcl-xL, which in healthy cells help to regulate apoptosis, but in cancer cells confer immortality [6]. In addition to this, other investigations have demonstrated that metformin triggers apoptosis by inhibiting cell proliferation proteins mTOR and Ras [7], and damages the glucose metabolism vital to cancer cells by blocking the function of hexokinase I/II enzymes [8].

Other studies have also shown that metformin activates the caspase family of endoproteases, which break down peptide bonds within molecules and are in turn involved in regulating cell death [9].

Statins

This group of drugs is routinely offered to 13% of the population ostensibly to lower blood cholesterol and reduce the risk of heart disease. However, like metformin, statins also seem to alter the expression of genes regulating the balance between life-promoting and death-promoting proteins in cancer, and may have a number of benefits in killing cancer cells.

A primary effect is that statins block activity of the cholesterol-producing enzyme HMG CoA, which means less cholesterol is available for the production of new cell walls in rapidly proliferating tumors.

Studies have shown statins also reactivate caspases, and act not only on abnormal Bcl-xL, but also on another protein involved in normal apoptosis termed Bax [10].

They also upregulate production of PPARGamma, another protein that programs cell death, which is knocked out by fast-replicating cancers [11]; and act to reduce the number of cell surface GLUT-1 glucose receptors, thus reducing cancer cell activity by limiting the amount of energy available [12].

Doxycycline

An antibiotic routinely used to treat acne, doxycycline is one of a number of similar agents that are showing benefits in cancer. It breaks down mitochondria, the energy-giving organelles found in super-charged cancer cells [13]. It also blocks the activity of metalloproteinases, which would otherwise be involved in the breakdown of the extracellular matrix that allows individual cancer cells to break free and seed new metastatic cancer growth around the body.

A complementary effect is that doxycycline also acts on abnormal Bcl-xL and reactivates caspase-3 and -9 to trigger cancer cell destruction [14].

Mebendazole

A compound originally developed as a treatment for parasitic worms, mebendazole works by fatally disrupting the cellular microtubule formation in abnormal cancer cells that occurs as the cell is attempting to divide. Like the other three compounds being used in this therapeutic approach, mebendazole also inactivates Bcl-2 and activates caspases to promote apoptosis in cancer cells, and the release of cytochrome c, which has also been shown to trigger apoptosis in malignant cells [15].

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When combined with low dose chemotherapy, there is also evidence these drugs help to destroy the tumor-associated macrophage cells that may help maintain a favorable environment for the cancer to flourish.

The evidence from these new studies suggests a potential benefit from taking these drugs alongside conventional cancer chemotherapy and immunotherapy, owing to the apparent symbiotic influence on the efficacy of each of them [16].

However, the authors of the studies have often implied that the benefits from this approach will not be available until a new generation of drugs is developed – a process that could take up to 10 years.

Major pharmaceutical players including Bayer, Pfizer and Astra Zeneca are all involved in developing new molecules or new combination adaptions of these treatments, which they hope to patent. However, it takes an average of 13.5 years to bring a new drug to the market, and only approximately 7% of the therapies entering Phase I trials make it all the way through to patients.

This log jam in access to currently available treatments has frustrated oncologists who are already pioneering the new approach and are anxious for it to be taken up by more treatment centers.

Despite the presumption they are legally entitled to offer treatments in the best interests of their patient, only a few oncologists are willing to pursue an approach of 'creative compassion' in their prescribing, and it is often hard for patients with terminal illness to seek out doctors willing to exercise such lateral thinking.

It is known among researchers with an interest in these therapies however, that there are National Health Service cancer specialists offering such drugs below the radar. Some speak privately of prescribing the antiviral valganciclovir for lymphomas in the brain and spinal cord, for example.

Others say that although they are aware of the new body of research, and the indications that such treatment prolongs lives, they do not use them for fear of criticism or hostility from colleagues towards anyone who strays beyond accepted practice.

One oncologist even cited the problem of insufficient time available in a standard 15-minute NHS consultation to allow an explanation of how the treatment might work.

Although the hope is that results from observational studies will provide enough convincing evidence for more of them to bring these drugs into routine use, those arguing for more immediate uptake believe many lives will be needlessly lost in the meantime.

Maybe it does not matter if the precise pathways are understood or not. If these treatments are safe and have a beneficial effect, many patients especially the dying ones, would say they should be used anyway.

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