



editorial



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Breaking away from the norm: a new perspective on cancer therapeutics

Cancer is one of the leading causes of death worldwide and the numbers are increasing year on year. As cancer diagnosis and treatment improves, however, more of these people will survive for longer than ever before, making decisions over the quality of life during and after treatment much more important [1].

Cancer chemotherapy: its effect and impact

Most cancer patients, especially those with advanced disease, receive treatment with a cocktail of cytotoxic drugs, many of which are associated with severe side effects, both in the short and longer term. These lead to dose reductions and delays in treatment and can even mean that treatment has to be stopped early, limiting the use of otherwise very effective drug regimens.

Cancer chemotherapeutics such as oxaliplatin increase the oxidative stress on cells. This is linked with a range of side effects including an impact on the blood-forming cells in the bone marrow, which increases the risk of infection [2,3]. Oxidative stress may also have a role in the development of chemotherapy-induced peripheral neuropathy [4] that impacts patients in the long term, persisting in up to 35% of patients five or six years after cessation of oxaliplatin-based treatment [5].

As an example, in colorectal cancer, the third most common cancer-related cause of death in the developed world, commonly used chemotherapeutic regimens include FOLFOX (folinic acid [leucovorin], fluorouracil and oxaliplatin). FOLFOX is usually dosed on alternate weeks. Because of the side effects, only around half of patients can tolerate 8–12 cycles of treatment and many cannot even cope with four cycles before the treatment has to be modified because of the extent of side effects.

Quality of life is key for patients

According to Cancer Research UK, there were 14.1 million new cases of cancer reported in 2012. This figure could increase to 23.6 million each year by 2030, an increase of 66% in low and medium human development index (HDI) countries and 56% in high and very high HDI countries [6]. Because diagnostics have become more sensitive, physicians are able to treat cancer at a much earlier stage, improving the chance of a positive outcome and long-term survival.

This is especially true for the cancers that affect children and young people. Overall, around two out of three people survive cancer for at least five years after diagnosis [1]; this rises to around 4 in 5 in cases of childhood cancer [7]. Of the 12 million or so cancer survivors in the US in 2012, at least 328,000 were diagnosed under the age of 21 [7]. As people are living longer, quality of life, particularly with respect to long-term and late effects of cancer treatment, is becoming a key issue for both physicians and patients. It will also be a concern for healthcare providers, in that as cancer survivors age any unexpected long-term effects on organs such as the heart, brain, kidneys and liver may become more apparent. Because of this, the authorities are also taking note, with quality of life becoming an important factor in pricing and reimbursement discussions. As a response, pharmaceutical companies will have to switch their focus away from chemotherapeutics that have an

impact on cancer in the short-term towards agents that provide quality of life both now and many years in the future.

Taking a different approach

Drug development is a long and costly process; it can cost up to \$350 million to take a drug from concept to launch, and take well over a decade. The figures are not quite as simple as that, however. Taking into account the number of drugs that fail, companies typically spend up to \$6.3 billion getting a successful drug onto the market.

The cancer market is a crowded and competitive one. At one end of the market, there are many older but still effective drugs available as lower cost generics, but that have drawbacks including the high levels of side effects and the development of resistance. At the other end, there are highly effective targeted therapeutics that have relatively lower levels of side effects. These are generally much more expensive, so treatment may not be affordable for all patients or payors and are only relevant to smaller groups of patients.

Rather than creating entirely new cancer chemotherapeutics, companies can cut development costs, risk and timescales by developing agents based on an already launched drug with a known safety profile. By focusing on developing drugs that can be used as an add-on to reduce the side effects of a range of commonly used regimens, small biopharma companies can create a niche market where the competition is not as fierce.

We are using this approach at PledPharma. Our lead product is PledOx (calmangafodipir), and rather than acting as a chemotherapeutic in its own right, we created it to work as a pretreatment before chemotherapy to reduce the side effects. PledOx is based on mangafodipir, a previously approved MRI contrast agent that has been found to mimic manganese superoxide dismutase and so has the potential to reduce oxidative stress on cells and it has been demonstrated to have both protective and anticancer effects [3].

MRI contrast agents have to be very low toxicity and mangafodipir has been used safely on more than 200,000 patients. However, they are designed for single administration. When used repeatedly, mangafodipir turned out to release large amounts of manganese, which can have toxic effects, particularly on the brain. PledPharma's drug developers have tailored mangafodipir by replacing much of the manganese with calcium, creating calmangafodipir, and this appears to be both safer and more effective. Even though there is an increased interest in repurposing and improving older drugs, there can be issues with patent protection and exclusivity. These modifications mean that we can also have secure levels of IP protection in place.

In animal studies, PledOx reduced myelosuppression in mice receiving oxaliplatin. Reducing the impact of chemotherapy on white blood cells reduces the risk of life-threatening infections, and suggests an additional role for the drug. The drug also increased the efficacy of oxaliplatin against the tumours [8].

Our initial focus is on reducing long-term peripheral neuropathy in patients receiving FOLFOX for colorectal cancer, and phase IIb clinical trials are under way. It also has potential in other cancers and with other regimens.

One of the key issues will be persuading oncologists that these agents will not reduce the efficacy of anticancer drugs, and perhaps even persuading patients who may believe that the side effects are an indication that the drug is working. While the anticancer effect is not a current focus, it acts as a reassurance for physicians and for patients that adding in another drug will not make treatment less effective.

Looking at the way ahead

There is an enormous market potential for companies that are looking to expand into combination therapies and different regimens. Working in niche areas, such as add-ons to cancer treatment regimens, is likely to be the way ahead, particularly for smaller biopharma companies that do not have the budgets of big pharma.

Companies working in new fields and niche areas have to 'break the ground' compared with existing therapeutic areas. However, there are more benefits than drawbacks, for example the opportunity to beat the competition and create a new market. Moving forward, the pharmaceutical industry also needs to see opportunities in combination therapies based on older drugs, for example packaging branded generics with complementary drugs such as PledOx.

References

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