The association between cancer treatments and dramatic side effects such as uncontrolled nausea and vomiting retains a powerful hold over public perceptions and parts of the media. Recent decades have seen a big improvement in many of these, partly due to advances in cancer therapeutics but also to innovations in supportive care. However new therapies have brought new challenges, particularly where patients receive multiple different types of treatment. “The side effect profile of treatments today is completely different from the past,” says Matti Aapro, oncologist at Clinique de Genolier in Geneva, with a special interest in supportive care, and current President of the European Cancer Organisation. It can still significantly impact on patients’ health and wellbeing, he says, and can alter the course of treatment in both the short and long term.

For conventional chemotherapy, “the standard [side effects] like nausea and vomiting, and neutropenia should be a thing of the past for the majority of the patients,” says Aapro. But with the introduction of targeted therapies and immunotherapies, there are new concerns.

Progress with ‘classic’ chemo side effects

Advances in treating chemotherapy-induced nausea and vomiting (CINV) have made these well-known side effects easier to manage, says Sergio Cantoreggi, Chief Scientific Officer of the Helsinn Group, a Swiss pharma company specialising in supportive cancer care. “Up to the late 80s, there were no truly effective antiemetics, and so people were getting combinations of drugs, [including] steroids, but they were not very effective.” But the introduction of 5-HT_3 antagonists such as ondansetron and later palonosetron have resulted in good control of vomiting, albeit with nausea remaining more problematic. A new class of antiemetic drugs that possess unique anxiolytic, antidepressant, and antiemetic properties is represented by neurokinin-1 (NK-1) receptor antagonists. The discovery of NK-1 receptor blockers was a crucial point in the prevention of emesis associated with cancer chemotherapy.

Helsinn have developed a combined capsule or infusion containing palonosetron and netupitant/fosnetupitant which is able to block both receptors. “That’s really unique, because you can combine both modes of action,” explains Cantoreggi, “and another important feature of this product is its long half-life, making it long acting… you are covered for the whole week.” The company is currently running studies on a paediatric formulation.

Neutropenia – depressed levels of neutrophils (phagocytic white blood cells) – is another classic, and potentially more dangerous, side effect associated with traditional cytotoxic treatment, where treatments have also improved. The recombinant granulocyte colony-stimulating factor filgrastim was among the first biologicals to be used in the care of cancer patients, getting approval from the FDA in 1991. But as Aapro points out, widespread access to this class of drugs is a more recent development. “[Biosimilar] drugs at lower prices has meant that they have been made available in many countries, without too many restrictions, so we have seen an increased uptake,” he says.

In February, the US regulators, the FDA, approved trilaciclib (Cosela), the first therapy in its class to treat chemotherapy-induced myelosuppression in small-cell lung cancer. Myelosuppression describes the damage to bone marrow cells which results in fewer red and white blood cells, leading to neutropenia, sometimes including fever. G1 Therapeutics’ clinical trials showed that, when administered intravenously prior to chemotherapy, only 11.4% of 123 patients on trilaciclib experienced severe neutropenia versus 52.9% of 119 patient in the placebo group.

New challenges

With the move away from reliance on cytotoxic drugs towards greater use of targeted therapies and immunotherapies came hopes that the days of debilitating side effects could be over. But, perhaps

inevitably, new treatment types have come with their own set of side effects. “There was this hype that immunotherapy isn’t chemo, it’s easier – well, yes and no!” says Aapro.

One of the most significant immune-related adverse events, associated particularly with EGFR inhibitors and some other agents, are skin disorders that can endanger patient health and the ability to continue on the therapy. A recent study, including approximately 15,000 patients taking immune checkpoint inhibitors, showed that 3.5% experienced these types of side effects and required hospitalisation, with younger patients, those taking multiple drugs and those with melanoma and kidney cancer at the highest risk.

“Even though new cancer treatments have less side effects, there are some that are still problematic,” agrees Raquel Abalo, a pharmacologist, from the Universidad Rey Juan Carlos in Spain. “Many people develop diarrhoea and this is probably one of the most dangerous side effects, because of the possibility of dehydration and electrolyte imbalance,” she says.

Because many cancer treatments disrupt the fast-dividing epithelial cells that make up the mucosa in the gastrointestinal tract, they are particularly vulnerable. This can also lead to oral mucositis – pain and ulcerative lesions in the mouth – which many patients find particularly debilitating. Furthermore, as Abalo points out, “[now] there are more and more survivors, which is of course very good, but we have to [monitor their side effects] for much longer.”

Mitigating damage to mucosa

One interesting new approach to treating oral mucositis is to use light. Spin-out company MuReva, working with researchers at the University of Buffalo School of Dentistry in the US, are using photobiomodulation to treat pain from oral mucositis and stimulate healing. Using light for healing is not new, but the Buffalo team have developed a new mouthpiece that allows light from a laser to target a large portion of the oral cavity in one go, treating the whole mouth in six minutes or less.

> A German team are developing an approach using UV light to treat the damage caused by checkpoint inhibitors to the colon mucosa

A German team are developing another approach using light – extracorporeal photopheresis, an established therapy for the treatment of graft-versus-host disease – to treat the damage caused by checkpoint inhibitors to the colon mucosa. This type of autoimmune colitis occurs in approximately one in five patients treated with combined checkpoint inhibitors, and the condition can become resistant to glucocorticoid therapy. Oncologist Robert Zeiser, from the University of Freiburg, is piloting its use in caring for cancer patients treated with immunotherapies. A patient’s white blood cells are treated with the drug 8-methoxypsoralen (8-MOP), which are then irradiated with UV light to activate, before being returned to the patient. 5-Methoxypsoralen is a naturally occurring furocoumarin that has been successfully used in combination with ultraviolet irradiation (PUVA) to manage psoriasis and vitiligo. PUVA 5-methoxypsoralen increases cutaneous photosensitivity. In the one patient given extracorporeal photopheresis after immunotherapy for metastatic melanoma, the colitis was completely resolved, where other approaches failed. Zeiser expects to publish further results this year.

Abalo has been looking at the potential use of cannabinoids for similar mucosal problems.

Cannabinoids target the endocannabinoid system, which includes receptors that are expressed throughout the central and peripheral nervous system. Currently the synthetic cannabinoid nabilone (Cesamet) is licensed to treat severe sickness caused by chemotherapy. There is a lot of anecdotal evidence related to cannabis and its efficacy in treating other side effects of cancer treatment, but few large enough trials to draw conclusions. Abalo also mentions animal studies which suggest that cannabidiol (CBD) could be useful, "but there is still a lot of work to do," she says.

> Abalo has looked at how cannabinoids might protect against mucosal damage that leads to diarrhoea and sometimes constipation, caused by vincristine

Abalo has looked at how cannabinoids might protect against mucosal damage that leads to diarrhoea and sometimes constipation, caused by vincristine (Oncovin). This chemotherapy drug is used to treat several types of leukaemia and small-cell lung cancer among others. It is known that cannabinoid receptors are over-expressed in some animal models of intestinal paralysis. Abalo found that a drug (AM251) was able to block one type of cannabinoid receptor involved in intestinal motility, and could partially prevent vincristine-induced constipation in rats.

Mitigating neuropathic side effects

Nerve damage and pain is one of the longer term side effects, particularly of platinum-based chemotherapies. "Neuropathic pain, the pain felt in hands or feet, while you are walking, or when you touch something, can be very, very painful and is a manifestation of the neurotoxicity of these drugs," explains Abalo. There has been some animal research into tempol – a drug molecule known since the 1990s to reduce neuropathic pain, due to its ability to decrease nitrogen oxide free radical molecules, which are involved in the development this type of pain.

Aapro mentions another approach used to try to mitigate neuropathic pain – cooling. "The use of gloves and socks that are frozen seems to prevent peripheral neuropathy a little bit… they are convincing enough for many centres to have adopted this type of prevention," he says. Known as continuous-flow limb hypothermia, this approach was evaluated in a 2017 study involving 20 breast cancer patients receiving paclitaxel in Singapore. The skin in one limb was cooled by 1.5°C for three hours during every infusion, and after six months they found a significant correlation between the cooling and less nerve damage. "It also works in the mouth, because the cold produces vasoconstriction… and you are going to limit the arrival of the cancer treatment to those areas," explains Abalo. The idea has also been exploited to try to reduce the hair loss caused by chemotherapy – a side effect that, though temporary, can impact heavily on people's self-image and self-confidence. Sadly cooling has not proven to be very effective in preventing hair loss according to Aapro, and better ways to manage this side effect are still needed.

Mitigating damage from radiotherapy

Cancer drugs are not the only sources of toxicity; radiation therapy comes with its own side effects, one of the most common being radiation dermatitis. Symptoms range from mild rashes to severe ulceration, and will be experienced by 85% of patients treated with this modality. While no effective treatments have yet been approved to treat this condition, Fred Ashbury, a supportive care specialist from the University of Toronto, and Editor in chief of Supportive Care in Cancer, the journal of the Multinational Association of Supportive Care in Cancer, points to important progress achieved in

limiting the damage in the first place. “The technology is more precise… mitigating a lot of the side effects of general radiation treatment,” he says. Better still, some therapies are now in development that may provide further relief. Matrix Biomed, based in California, is carrying out clinical trials for radiation-induced dermatitis, with several formulations of tempol (MTS-01), based on its ability to scavenge free radicals and protect cells against radiation-induced DNA damage. In their phase II studies no MTS-01 treated patient developed severe radiation dermatitis and phase III trials have now been approved.

US company Galera Therapeutics recently received a fast track approval designation from the FDA for its drug candidate avasopasem manganese (GC4419), which aims to reduce radiation- and chemotherapy-induced oral mucositis in patients being treated for head and neck cancers. The drug mimics the action of enzymes that remove free radicals from the body. So far the drug has successfully completed two clinical trials and demonstrated a 92% reduction in median duration of serious oral mucositis and reductions in incidence and severity of 34% and 47% respectively.

Amifostine reduces renal toxicity, but is also used to prevent dry mouth symptoms caused by radiation in patients with head and neck cancer

One chemotherapy and radioprotective drug already in use is amifostine, which reduces renal toxicity, but is also used to prevent dry mouth symptoms (xerostomia) caused by radiation in patients receiving treatment for head and neck cancer. There is ongoing research into other radioprotective molecules, including a recent report from the Institute of Radiation Medicine in Tianjin, China, who are developing a nanoscale polymer delivery system that would release its protective drugs only in the presence of harmful free radicals. The nanoparticles contain several active ingredients, including curcumin – the compound found in the spice turmeric, known for its anti-inflammatory and anti-oxidant properties and used in traditional Indian medicine.

For patients at later stages, the toll of the disease and treatment can lead to cancer anorexia and cachexia. “It’s very common in some cancer types,” says Cantoreggi. “You lose appetite, you lose strength, you lose the ability to tolerate chemotherapy and you lose quality of life.” In pancreatic cancer more than eight in ten patients develop anorexia-cachexia and it’s also common in people with advanced lung and colorectal and gastric cancers. Helsinn have developed a treatment, anamorelin, based on the appetite hormone ghrelin. “In cancer patients, ghrelin levels can be depressed, and anamorelin is a ghrelin agonist so it mimics its effects… [patients] put on weight, they feel better and they can potentially tolerate chemotherapy better,” explains Cantoreggi. “Unfortunately, it’s not a magic bullet, but we have seen very good data in large clinical trials, showing a sustained improvement of appetite, body weight and quality of life.” The product has been approved in Japan and the company hopes to make it available in other regions in the near future.

New solutions to side effects are being developed, but it is widely perceived to be a neglected area within cancer research. “If you go on the on a database for drug in development in cancer, probably 98% are therapeutics, and there’s very little in supportive care,” says Cantoreggi. “I don’t think the balance is right, but I think the balance is shifting,” says Ashbury. He points out that, while treating side effects may seem peripheral, if they end up preventing or interfering with treatment, then clearly they need addressing. Aapro say he was pleased to see that the European Union cancer research ‘Cancer mission‘ for solving societal challenges, developed in 2020, includes supportive care, “Whether this translates into supporting grants for research [into treating side effects] remains

to be seen," he adds.

Supporting clinicians to support patients

Aapro emphasises that part of the problem behind poorly controlled side effects is not just a lack of innovative treatments but a lack of knowledge and awareness among clinicians about the latest guidelines. "Unfortunately, the side effects of cancer treatments, whether from surgery, radiation, or medical oncology treatments, are still in my opinion poorly treated, because of insufficient training of the physicians, and also of the nurses, who often act as the interface between the physician and the patient." Ashbury agrees, "We haven't improved the knowledge base to use these tools as effectively perhaps as we should… and it's no different whatever part of the world you're in."

It doesn't help that, over the last 20 years, the range of different treatments have mushroomed, as have the range of side effects that come with them. As Ashbury points out, while thirty years ago there may have been 70 drugs available to treat cancer, a similar number were approved by the FDA and EMA in 2020 alone. "You're asking your typical oncologist, who is seeing many patients every day, to now be aware of these new drugs [and] these new toxicity management strategies… it's like the cockpit of a 747."

Early or prophylactic treatment is often important in treating side effects, but it can be hard for clinicians to identify which patients may need early intervention. "We have some idea," says Aapro, "If you look at elderly patients, there are algorithms that allow you to predict who is at a higher risk of toxicity… if a patient is malnourished, we know that there's an increased risk of at least surgery- or chemotherapy-related side effects." A recent randomised controlled trial run by oncologist Daneng Li from the City of Hope National Medical Center, in Duarte, California, showed that, when a 'Geriatric Assessment-driven Intervention' (GAIN) process is implemented to address chemotherapy toxicity in older cancer patients, patients experienced an almost 10% reduction in chemotherapy-related toxicity.

> "Patients also often go through several rounds of different treatments now, which can complicate their side-effect responses"

Another more recent complication is the side effects resulting from being treated with multiple kinds of drugs. "Combinations are to some extent a new frontier; they can help from an efficacy standpoint, but they may also complicate the side effect profiles significantly," says Cantoreggi. Ashbury points out that patients also often go through several rounds of different treatments now, which can complicate their side-effect responses. He mentions the example of HER2+ breast cancer patients, "We discovered that for patients who had been previously treated with cytotoxics, moving onto trastuzumab had a much greater risk of cardiotoxicities."

Ashbury is also keen for the side effects of cancer treatments to be understood in a wider context, considering emotional and spiritual health on top of purely biological concerns. "We [do now] have a more sophisticated approach to psychosocial challenges; we have better interventions for insomnia, for instance." Ashbury suggests that the 'financial toxicity' of cancer treatment should also be taken account of as a side effect. "I don't want us to lose sight of the fact that this has become a very important challenge for us. With these [expensive] novel agents… in some countries, it will be [financially] intolerable for [patients to] access to them."

As treatments for cancer improve and survival rates increase, the question is whether we might one day achieve side-effect free treatments? “I regret to say that I believe that the side effects will continue to exist,” says Aapro. Most mechanisms to kill cancer cells will have some spillover to healthy cells, and that seems unlikely to change.” He stresses, however, that huge improvements are possible through raising awareness and educating not just clinicians but also patients. “We have already developed better ways to treat and control side effects, we need to teach patients and the public at large that they can demand treatment with less side effects.”

Illustration by Maddalena Carrai

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