The transformation of chemotherapy by the 5-HT3 antagonist ondansetron

Our latest article on landmark drugs from Jenny Bryan looks at how ondansetron emerged from a research programme in the mid-1980s and was shown to be more effective than older antiemetics in controlling nausea and vomiting for patients undergoing chemotherapy.

Before the arrival of the first 5-hydroxytryptamine-3 (5-HT3) antagonist ondansetron (Zofran) in 1990, most patients undergoing cancer chemotherapy expected to be sick, and many of those taking particularly emetogenic drugs, such as cisplatin, were very sick indeed. Some became so dehydrated that they needed extra days in hospital to restore their fluid balance or had their cancer treatment disrupted or delayed because they were too ill to continue.

Lorraine Hyde, medical day care unit matron at the Royal Marsden Foundation Trust, Sutton, Surrey, remembers trying to coax testicular cancer patients to drink a little water to try to prevent renal problems if they became too dehydrated as a result of vomiting during their cisplatin treatment.

"As a young nurse, I was very affected by the sight of these young men who we knew could be cured by the cisplatin, but were so sick as a result of the treatment. We gave them lorazepam and antiemetics, such as metoclopramide, dexamethasone and cyclizine to try to help, but they weren’t very effective," she says.

Linking the gut to the brain

GR38032F (ondansetron) emerged from a research programme at Glaxo’s laboratories in the mid-1980s, which aimed to discover compounds that were active at 5-HT3 receptors on neurones of both the peripheral and central nervous systems. Earlier studies had suggested that the antiemetic effects of metoclopramide were partly mediated through 5-HT3 antagonism, but the drug’s dose-limiting extrapyrimidal side effects related to its activity at dopamine receptors meant that it could not be used effectively with the most emetogenic regimens.

In contrast, ondansetron was shown to be a potent and selective antagonist of 5-HT3 receptors, whose role in emesis was linked to their presence on the vagus nerve in the gastrointestinal tract and the area postrema (vomiting centre) in the brain. It was proposed that serotonin released by the enterochromaffin cells of the small intestine, in response to chemotherapeutic agents, stimulated 5-HT3 receptors on vagal afferent nerves which, in turn, stimulated the area postrema in the brain to trigger vomiting. By blocking 5-HT3 receptors in the intestine and the area postrema, ondansetron was thought to interfere with the neuronal circuitry involved in the vomit reflex.

Clinical benefits

In clinical trials, ondansetron soon demonstrated its superiority over metoclopramide in controlling acute emesis and nausea associated with cisplatin chemotherapy. Of patients given ondansetron, 65–75 per cent achieved complete or major control of emesis (two or fewer episodes of emesis), compared with 41–55 per cent of patients using metoclopramide. In European studies, 58–74 per cent of patients given ondansetron reported no or mild nausea compared with 42–67 per cent treated with metoclopramide.

Subsequent studies showed that the antiemetic effects of ondansetron in cisplatin-treated patients could be enhanced by adding dexamethasone, with complete or major.

Most patients undergoing cancer chemotherapy expected to be sick, and some became dehydrated as well (Mark Thomas/Science Photo Library)
“The fact that we can now give even platinum-based treatment on a day-case basis just shows what a major impact ondansetron and granisetron have had”

responses achieved in 69–97 per cent of patients, compared with 56–81 per cent of patients when ondansetron was used on its own.6,7 Clinical trials also showed that ondansetron was more effective than older antiemetics in controlling the acute and delayed onset nausea and vomiting associated with cyclophosphamide-based chemotherapy used to treat breast cancer9 and radiotherapy-induced emesis. By this time, Roche had launched rival 5-HT3 antagonist granisetron and there was intense competition between Roche and Glaxo to prove the superiority of their product. Because the first head-to-head study showed comparable antiemetic efficacy and tolerability for the two drugs,9 the manufacturers had to settle for equivalence, although the rivalry to show greater cost-effectiveness continued.

Balancing efficacy against cost

With the price of ondansetron and granisetron far higher than that of metoclopramide, both Glaxo and Roche needed to convince budget holders that controlling nausea and vomiting was an essential component of cancer therapy, not a luxury.

“In those days, patients had their chemotherapy as inpatients, and there was a good financial argument for controlling their sickness, so they didn’t need to spend extra time on the wards. But clearly it would have been a waste of money to give the new drugs to patients whose chemotherapy was unlikely to make them sick, so there was a process of education to make sure that the drugs were used correctly,” recalls Ms Hyde.

A study carried out at the Royal Marsden supported the cost-effectiveness argument, showing that the cost per successfully treated patient (one emetic episode or none, and no adverse events) was £95.20 for ondansetron, compared with £92.18 for metoclopramide.10

In some parts of the UK, progress was slow and, initially, some health authorities restricted treatment to those who had already been very sick during earlier cycles of treatment. Ms Hyde explains that some people are more prone to chemotherapy-induced emesis, with women more likely to be sick than men, younger patients than older patients, and those with a history of motion sickness also at greater risk. However, pharmaceutical companies argued that, by the time cancer teams discovered whether a patient was prone to sickness, it was already too late. If they vomited during their first cycle of chemotherapy, it would be much harder to stop them vomiting in subsequent cycles, even with 5-HT3 antagonist treatment, they argued.

“Even the smell of chemotherapy makes some people feel sick, and the rationale has to be prevention,” agrees Ms Hyde. “It’s an uphill battle once people have already started vomiting, so the briefing has to be on trying to prevent them from vomiting in the first place.”

Other indications

As the economic arguments supporting ondansetron and granisetron alone or in combination with dexamethasone gradually took hold in chemotherapy-induced emesis, clinical trial data were being published demonstrating the benefits of 5-HT3 antagonists to prevent postoperative nausea and vomiting (PONV). But, again, cost was a significant issue.

A large systematic review showed that ondansetron was more effective than metoclopramide in preventing PONV, and comparable to droperidol.11 A more recent Cochrane review concluded that droperidol, metoclopramide, cyclizine, dexamethasone, ondansetron, granisetron and the newer 5-HT3 antagonists tropisetron and dolasetron were all more effective than placebo in preventing PONV but that publication bias made it difficult to demonstrate differences between the drugs.12

Research has continued to investigate the use of 5HT3 antagonists in further indications, including anxiety disorders, irritable bowel syndrome and, combined with haloperidol, in treatment-resistant schizophrenia. But, with generic versions of both the leading agents, ondansetron and granisetron, now available, it seems unlikely that any further large, licensing trials will be carried out.

Lasting legacy

The 5-HT3 antagonists cannot prevent every cancer patient from feeling sick when he or she has chemotherapy. They have undoubtedly revolutionised cytotoxic administration. Today, they are a key part of the holistic approach to emesis prevention used on cancer wards, which includes advice on overcoming chemotherapy-induced smell and taste changes that can contribute to sickness problems.

As Ms Hyde points out, patients no longer arrive for chemotherapy in fear of sickness. They know that their nausea and vomiting can be controlled with drugs, intravenously during their chemotherapy infusion, and orally when they go home.

“The fact that we can now give even platinum-based treatment on a day-case basis just shows what a major impact ondansetron and granisetron have had,” concludes Ms Hyde. “We know that we can control sickness while we are giving chemotherapy to our patients, and we aren’t worried that they will have uncontrolled vomiting when they get home. It’s a huge success story.”

References


