Development of Ondansetron

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Summary

The rapid development of 5-HT₃ receptor antagonists such as ondansetron has resulted in a major advance in the management of cancer chemotherapy and radiotherapy-induced emesis with many patients throughout the world now benefiting from this innovation. However, the inevitable consequence of such a rapid development is that some unresolved scientific and clinical issues remain and merit review and discussion at ECCO meetings [1,2]. The ondansetron clinical database includes information on more than 14,000 patients in clinical trials.

Furthermore, over half a million cancer patients have received the drug in clinical practice. This clinical experience has produced information on dosing, efficacy and the side effects of the drug. It is clear that the mechanism of action of ondansetron involves both central and peripheral 5-HT₃ receptors although the relative importance of each receptor site remains unresolved. As anticipatory emesis is probably of psychogenic origin, the effect of ondansetron is less predictable. Ongoing trials should resolve the place of ondansetron in the prevention or treatment of anticipatory emesis, although improved control during the first cycle of chemotherapy should ultimately reduce the scale of this problem.

Pharmacology and Clinical Profile

Dr. Brown was able to show that a single intravenous dose of ondansetron (8–32 mg) was equal in efficacy to standard regimens based on an 8 mg loading dose followed by a 24-hour infusion in patients given high-dose cisplatin. The results clearly supported the use of single doses in the range 8–32 mg, depending on the degree of emetogenic challenge [3]. As a single dose of ondansetron is equal in effect to a continuous infusion in the prevention of cisplatin-induced acute emesis, constant plasma concentrations and the half-life appear unrelated to antagonism of the emetic reflex. Ondansetron is highly selective for the 5-HT₃ receptor and shows little or no affinity for other receptors. It is reasonable to conclude that ondansetron's 5-HT₃ receptor antagonist activity is directly responsible for its clinical effects.

Clinical Trial Methodology

Historically, anti-emetic trials were not always directly comparable due to a general lack of good methodology principles and consistent measurement criteria. The Phase III programme for ondansetron has followed well-established principles of randomised, double-blind, parallel-group design, stratified to balance known prognostic factors such as sex, prior alcohol intake and previous experience of emesis.

Paediatric Cancer

Treating children with cancer is a particularly demanding situation for all concerned. As aggressive, highly emetogenic chemotherapy is usually employed in pursuit of a cure, the need for effective anti-emetic control is paramount. Ondansetron has been shown to be highly effective in this group of patients and the absence of extrapyramidal side effects is a significant

advantage in children who are particularly susceptible to these effects when given dopamine antagonists, such as metoclopramide.

Quality of Life Benefits

Although the efficacy of ondansetron is normally measured purely in terms of the control of emesis and nausea, the benefits in quality of life are being confirmed through systematic study.

Dr. Kaasa focussed on the practical problems of collecting quality of life data using either personal interviews or questionnaires.

The questionnaires are more appropriate for multicentre trials, where the use of a well validated instrument such as the FLIC or Rotterdam Symptom Checklist is essential. A key point is the timing of data collection and the importance of measuring parameters immediately before and after chemotherapy.

The treatment of breast cancer is a major challenge to oncologists. A comprehensive study using repeat cycles of chemotherapy confirmed superior and sustained efficacy of ondansetron over the 6 cycles compared to metoclopramide, with important measurable benefits in terms of improved quality of life.

Comparisons with Standard Anti-Emetics

The majority of comparative studies using ondansetron have included metoclopramide as the standard reference based on its status as the most widely used single anti-emetic. Alizapride is also widely used in much of Europe, so it is of interest to observe the results of a comparison between ondansetron and a combination of alizapride and methylprednisolone in patients receiving cisplatin chemotherapy. Ondansetron was shown to be superior in efficacy to alizapride/methylpred-nisolone (88 vs. 63% of patients with complete or major control) and produced a higher degree of patient satisfaction (83 vs. 56%).

The Role of the Cancer Nurse

It is important to recognise the key role played by specialist cancer nurses in the management of emesis. The trend towards a well integrated care plan for cancer patients is evident with the nurse in a pivotal position to observe the results of good or poor anti-emetic control.

Ondansetron is now becoming included in routine anti-emetic protocols and is providing real benefits to doctors, nurses and their patients through regular use.

Conclusions

Although a complete understanding of the emetic pathways and, by inference, the ability to completely block the emetic reflex, remains an elusive objective, the outstanding efficacy of ondansetron, well supported by a multitude of clinical trials and patient experience, has helped in improving our understanding of the emetic pathways affected by cytotoxic treatment for cancer. Further studies will help to further optimize the role of ondansetron in the control of acute, delayed and, perhaps, anticipatory emesis.

References

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