Chemotherapy-induced nausea and vomiting are ranked by the patients as two of the most troublesome adverse effects. Consequently a large number of trials comparing different antiemetic regimens have been published during the past twenty years. The vast majority of these trials have included patients receiving their first course of cisplatin-based or cyclophosphamide-anthracycline (AC)-based chemotherapy. Clinical guidelines are therefore very specific and the level of evidence is high, when recommendations for antiemetic prophylaxis are given in patients treated with cisplatin- or AC-based chemotherapy [1].

The study by Abbrederis et al. [2], published in this issue of Onkologie is interesting because it included patients with cancer of the gastrointestinal tract – a study population rarely addressed in antiemetic trials. Furthermore a sub-population of patients with refractory emesis (emesis in the previous course of chemotherapy) was investigated. Abbrederis and colleagues found that the majority of patients (85%) obtained adequate antiemetic protection in cycle 1 with a regimen including a serotonin (5-HT₃)-receptor antagonist (day 1) plus dexamethasone (day 1–3). 15 out of 81 patients (18.5%) receiving low-dose cisplatin (< 50mg/m²) suffered from nausea and vomiting, confirming the high emetic risk potential [1] of this regimen. Contrary to this, only 1 out of 25 patients (4%), receiving the new platinum compound, oxaliplatin, experienced acute (day 1) and delayed (day 2–5) nausea and vomiting. 2 other studies, until now published as abstracts only, investigated antiemetic efficacy in patients treated with oxaliplatin-based chemotherapy [3, 4]. In the first study in which patients did not receive antiemetics beyond day 1 of chemotherapy [3], Hesketh et al. reported that among patients treated with oxaliplatin (85–100 mg/m²), 97% were completely protected from acute emesis, but that 51% of the patients vomited and/or needed rescue antiemetics in the delayed phase. In a randomized, double-blind phase II study the addition of the NK₁-receptor antagonist, casopitant (day 1–3), to a combination of ondansetron (day 1–3) plus dexamethasone (day 1) was investigated in patients receiving moderately emetogenic chemotherapy [4]. In a subpopulation (n = 123) treated with oxaliplatin-based chemotherapy, the 0–120-h complete response rate (no emesis and no need for rescue antiemetics) was improved from approximately 70% to approximately 80% by addition of casopitant. The three studies strongly suggest that patients treated with oxaliplatin-based chemotherapy need antiemetic prophylaxis for both acute and delayed nausea and vomiting [2, 3]. A combination of a serotonin antagonist plus dexamethasone will provide sufficient antiemetic effect in the majority of patients [2–4], an effect that can be slightly improved by addition of the NK₁-receptor antagonist casopitant [4].

In the Abbrederis study, 11 patients with refractory nausea and vomiting in course one seemed to benefit from the addition of the NK₁-receptor antagonist, aprepitant, in subsequent cycles of the same chemotherapy. The small number of patients and the design of the study make more in-detail conclusions irrelevant. 2 other non-randomized studies have investigated aprepitant in patients with refractory nausea and vomiting [5, 6]. Both found that aprepitant optimized the antiemetic effect in patients receiving a combination of an anthracycline plus cyclophosphamide [5] and in patients receiving different regimens of moderately or highly emetogenic chemotherapy [6]. Randomized, double-blind studies have demonstrated that patients with refractory emesis in the first course of chemotherapy can benefit from the addition of an antiemetic with another mechanism of action in subsequent courses [7–9]. For instance, the addition of the dopamine (D₂)-receptor antagonist, metopimazine, improved the antiemetic effect of ondansetron [7] and of ondansetron plus methylprednisolone [8] in patients with refractory emesis. Furthermore, patients receiving moderately emetogenic chemotherapy and refrac-
tory to antiemetic prophylaxis with granisetron or a combination of prednisolone plus metopimazine, did significantly better if the 3 antiemetics were combined in subsequent cycles of the same chemotherapy [9].

The randomized, double-blind study design is particularly important, when investigating patients with refractory nausea and vomiting. In a large study (n = 338) in patients receiving cisplatin-based chemotherapy and refractory to antiemetic therapy with ondansetron plus methylprednisolone, as many as 38% of the patients in the control arm did not vomit in the subsequent cycle, despite receiving the same antiemetic prophylaxis as in the previous course [8]. This emphasizes that the effect obtained in refractory patients investigated in non-controlled studies can be considerably overestimated.

The study by Abbrederis et al. is important because it addresses some of the orphan and difficult topics in antiemetic research. Evidence-based antiemetic recommendations are not always implemented in the daily clinic. One of the barriers to the implementation is the fact that guidelines lack inclusion of many clinically relevant patient populations. Systematic implementation of guidelines will therefore necessitate initiation and completion of ‘difficult studies’. These studies need to focus on the entire course of chemotherapy (multiple cycle studies), include patients receiving chemotherapy during several days (multiple-day studies), patients receiving new antineoplastic agents and new molecularly targeted therapies. Furthermore the number of patients receiving combined radio-chemotherapy is rapidly increasing and needs special attention.

References