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Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany

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ABSTRACT

Background: Chemotherapy-induced nausea and vomiting (CINV) remains a major adverse effect of cancer therapy. We aimed to determine outcomes associated with use of aprepitant in outpatients undergoing highly emetogenic chemotherapy in Germany from a patient's and payer's perspective.

Methods: A decision–analytic model compared an aprepitant regimen (aprepitant/ondansetron/dexamethasone) to a control regimen (ondansetron/dexamethasone) over a five days period. Clinical results and resource utilisation observed in aprepitant phase III clinical trials were assigned German unit cost data.

Results: Complete response over one chemotherapy cycle was observed in 68% of patients in the aprepitant group ($N = 514$) compared to 48% of patients in the control group ($N = 518$). Patients were estimated to have gained an equivalent of 15 additional hours of perfect health per cycle (0.63 quality-adjusted life days) with aprepitant-based regimen compared to control regimen. Cost per quality-adjusted life year gained with aprepitant was estimated at €28,891.

Conclusions: Aprepitant substantially improved CINV-related health outcomes in patients undergoing highly emetogenic chemotherapy. Incremental benefits materialised in a cost-effective fashion.

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) remains a major adverse effect of cancer chemotherapy despite the availability of a variety of antiemetic drugs including 5-hydroxytryptamine 3 (5-HT_3) receptor antagonists. CINV has a considerable impact on patients' quality of life and is the adverse effect most feared by patients receiving chemotherapy.[1,2]

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Although 5-HT_3 receptor antagonists themselves act to prevent acute CINV (CINV within 24 h after chemotherapy administration), better control is achieved in combination with dexamethasone. This treatment combination was shown to completely prevent acute CINV in about 75% of high-risk cisplatin-treated patients.[3] However, 5-HT_3 receptor antagonists are not effective against Cisplatin-induced delayed CINV (more than 24 h after chemotherapy).[4] Delayed nausea and vomiting were observed in 60% and 50% of patients treated with highly emetogenic chemotherapy, respectively.[5–7] Despite this, greater than 75% of physicians and nurses underestimated the incidence of delayed CINV developing on days 2–5 following chemotherapy.[5]

Aprepitant (Emend™) is a highly selective non-peptide neurokinin-1 receptor antagonist which represents a new approach to antiemetic therapy. Efficacy of aprepitant was investigated during a period of five days following chemotherapy in two randomised phase III clinical trials.[8,9] Clinical studies have shown that aprepitant improved the protection against CINV provided by therapy with ondansetron plus dexamethasone over multiple cycles of highly emetogenic cisplatin-based chemotherapy.

Cancer patients in Germany receive highly emetogenic chemotherapy as either in- or outpatients, depending on regional availability and the patient's medical condition and preferences. There is a trend toward the outpatient setting, both at hospitals (day clinics) and office practices, therefore we based our analyses on outpatients. The perspective was that of the statutory health insurance funds (SHI).

A decision–analytical model was developed using aprepitant clinical trial data and German cost data. In oncology, cost per life year saved and cost per quality-adjusted life year (QALY) saved are common measures. QALYs account for changes in both life expectancy and the patient's health state and provide a common platform for comparisons of health interventions in oncology and other fields. In the present study, effective antiemetic prophylaxis was regarded as contributing to a marked improvement in quality of life without improving survival in the short or long term. The objective of this analysis was to estimate the health benefits, costs, and cost per QALY of aprepitant combined with a 5-HT_3 receptor antagonist and dexamethasone compared to a control regimen (a 5-HT_3 receptor antagonist and dexamethasone) for outpatients undergoing highly emetogenic chemotherapy in Germany.

2. Patients and methods

2.1. Study population

Data were pooled from a combined analysis of two multicentre, randomised, double-blind phase III clinical trials comparing aprepitant regimens (day 1: aprepitant in combination with ondansetron plus dexamethasone, days 2–3: aprepitant plus dexamethasone, day 4: dexamethasone alone) to a control regimen (day 1: ondansetron plus dexamethasone, days 2–4: dexamethasone alone) in multiple cycles of cisplatin-based (cisplatin $\geqslant$70 mg/m^2) chemotherapy[10] (Table 1). These trials included patients with the following primary cancer diagnosis respectively: respiratory (42%), urogenital (23%) and other (35%); respiratory (37%), urogenital (38%), eyes/ears/nose/throat (8%) and other 17%.[8,9] The analysis used a combined exploratory endpoint of no emesis and no significant nausea (*i.e.* nausea which interfered with a patient's normal activities) over five days following cisplatin. These data reflected a modified intent-to-treat (MITT) population consisting of those patients who were randomised, received cisplatin and at least one dose of study drug, and underwent at least one post-treatment assessment. Baseline characteristics, reasons for discontinuation, and drop-out rates were similar between groups. Compared to the control group ($N = 522$), patients in the aprepitant group ($N = 516$) were more likely to remain free of emesis and of significant nausea (complete protection) during the first (61% *versus* 46%, $p < 0.006$) and subsequent cycles in intention-to-treat analyses.[10] For the current evaluation, randomised patients were required to meet the following conditions: (i) patient received cisplatin-based chemotherapy, (ii) patient received at least one dose

Table 1 – Phase III trials of aprepitant with control regimen versus control alone

Regimen[a]	Day 1	Day 2	Day 3	Day 4
Control regimen (518 patients)	Placebo	Placebo	Placebo	
	Ondansetron (32 mg IV)	–	–	–
	Dexamethasone (20 mg PO)	Dexamethasone (16 mg PO)	Dexamethasone (16 mg PO)	Dexamethasone (16 mg PO)
Aprepitant regimen (with control) (514 patients)	Aprepitant (125 mg PO)	Aprepitant (80 mg PO)	Aprepitant (80 mg PO)	–
	Ondansetron (32 mg IV)	–	–	–
	Dexamethasone[b] (12 mg PO)	Dexamethasone (8 mg PO)	Dexamethasone (8 mg PO)	Dexamethasone (8 mg PO)

a All regimens administered 30 min prior to chemotherapy, except aprepitant (60 min).
b In pharmacokinetic studies, aprepitant increased the area under the concentration curve (AUC) of dexamethasone, thus dexamethasone dosage was reduced: 12 mg on day 1, 30 min prior to chemotherapy, and 8 mg once daily on days 2–4, in aprepitant regimen.

of study drug, (iii) patient had at least one post-treatment assessment, and (iv) patient had complete healthcare resource utilisation records. There were 514 patients in the aprepitant group and 518 patients in the control group available for analysis.

2.2. *Perspectives*

The analysis was conducted for patients receiving chemotherapy as outpatients at office-based facilities from the patient and statutory health insurance perspective. The statutory health insurance perspective also includes the consideration of hospitalisation cost.

2.3. *Decision–analytic model*

A decision–analytic model was constructed in Microsoft Excel™ (2002) to compare the aprepitant regimen to control regimen over a single cycle of chemotherapy. Fig. 1 depicts the model structure. The model's health states were based on the clinical endpoints in the clinical trials.

- Complete protection: no emesis, no rescue therapy, and maximum reported nausea <25 mm measured on a 100 mm visual analogue scale.
- Complete response at best: no emesis, no rescue therapy, and a maximum reported nausea ⩾25 mm measured on a 100 mm visual analogue scale.
- Incomplete response: the complement of the preceding states: some emesis or rescue therapy.

Model state probabilities based on the observed number of patients from the modified intention-to-treat population in each health state are shown in Table 2.

2.4. *Utilities*

Utilities are used as a measure to describe preferences individuals or society may have for any particular set of health outcomes. To account for the less than perfect health of patients with CINV, published patient preferences (utilities) were reevaluated and assigned to each health state in the cost-effectiveness model. Grunberg *et al.*[11] evaluated utilities

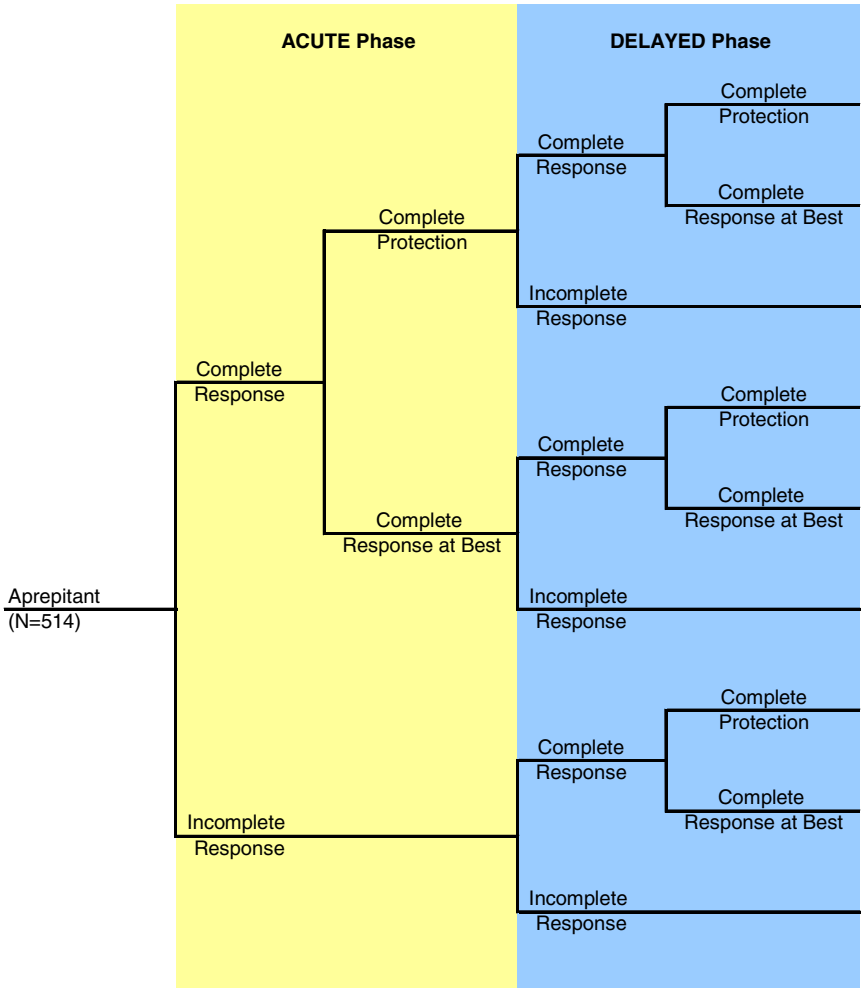

Fig. 1 – Model structure. Identical structure in the aprepitant and control arm. Complete protection: no emesis, no rescue therapy, and maximum reported nausea <25 mm measured on a 100 mm visual analogue scale. Complete response at best: no emesis, no rescue therapy, and a maximum reported nausea ⩾25 mm measured on a 100 mm visual analogue scale. Incomplete response: the complement of the preceding states: some emesis or rescue therapy.

Table 2 – Health state probabilities based on modified intention-to-treat analysis of two phase III clinical trials (052/054)

Health states by phase		Aprepitant regimen (n = 514)		Control regimen (n = 518)	
Acute phase (day 1)	Delayed phase (days 2–5)	n	%	n	%
Complete protection	Complete protection	306	59.5	231	44.6
	Complete response	29	5.6	8	1.5
	Incomplete response	88	17.1	121	23.4
Complete response at best	Complete protection	4	0.8	2	0.4
	Complete response	8	1.6	5	1.0
	Incomplete response	6	1.2	12	2.3
Incomplete response	Complete protection	17	3.3	13	2.5
	Complete response	3	0.6	5	1.0
	Incomplete response	53	10.3	121	23.4

Model health states described in Table 3.

using a visual analogue scale for chemotherapy states in the absence and presence of nausea and vomiting. Borjeson *et al.*[12] used the same scale to assess nausea in patients undergoing chemotherapy. Sun *et al.*[13] used visual analogue scales (VAS) as well as time-trade-off (TTO) techniques to evaluate patient preferences regarding side effects of high-dose chemotherapy. All three sources were considered. Initially, an anchor utility for chemotherapy without nausea and vomiting was determined. Although Sun *et al.* assigned this state a utility of 1.000, Borjeson *et al.*'s 'chemotherapy with no nausea' state (0.993) and Grunberg *et al.*'s 'chemotherapy with no nausea/vomiting' state (0.790) may better reflect the fact that chemotherapy without such side effects is less than perfect health. We therefore assigned a utility of 0.9 to the model health state 'complete protection' which corresponds to chemotherapy with no appreciable nausea or emesis. For the 'incomplete response' health state, in which emesis and/or nausea is present, the utility value was set at 0.2 (approximately equal to Sun *et al.*'s elicited preference for this state). In the 'complete response at best' model state, a patient has no emesis or rescue medication, but may have a small amount of nausea. We used the utility for the mild nausea state from Borjeson *et al.* (0.752), normalised to our 'chemotherapy without nausea and vomiting' anchor value of 0.9, to develop the utility for our 'complete response at best' health state equal to 0.7 (Table 3).

2.5. *Health outcomes*

The main outcome measure was the percentage of patients who had neither emesis nor rescue therapy over the entire 5-day cycle (complete response). To that end, the health states for the acute phase (day 1) and for the delayed phase (days 2–5) were assessed and 'complete response' was characterised as the absence of incomplete response in both, the acute and the delayed phase. Further health outcomes included the number of emetic events, the number of emesis-free and CINV-free days, the percentage of emesis-free and CINV-free patients, and the percentage of patients with no impact on daily life due to CINV. The functional living index-emesis was used to assess the patient-reported impact of CINV on daily life.[14] Quality-adjusted life days over the entire 5-day observation period were determined by multiplying the number of days spent in each health state by the respective patient preference values. In Table 4, we show the projected decrease in quality-adjusted life days from perfect health associated with each CINV health state combination at the end of five days following chemotherapy.

2.6. *Resource utilisation and costs*

Resource utilisation data were collected alongside the aprepitant phase III clinical trials. Costs of resources were determined using German unit cost from the statutory health insurance perspective.[15–18] Unit costs of antiemetic prophylaxis, rescue medication, and hospitalisations are reported in Table 5. Because manufacturer rebates and patient co-payments have undergone frequent changes and are a subject of ongoing discussion in Germany, drug costs were not reduced on this basis. Due to the short time frame, we report in undiscounted year 2004 EUROs.

2.7. *Sensitivity analysis*

Sensitivity analyses were performed to investigate the robustness of the results to variability in the efficacy of aprepitant in terms of the proportion of complete responders. The differ-

Table 3 – Patient preferences (utilities) by model health state

Health state	Description	Utility
Complete protection	No emesis, no rescue therapy, and maximum nausea < 25 mm on a 100 mm visual analogue scale	0.9
Complete response at best	No emesis, no rescue therapy, and maximum nausea ⩾25 mm on a 100 mm visual analog scale	0.7
Incomplete response	Some emesis and/or rescue therapy	0.2

Table 4 – Number of quality-adjusted life days expected at the end of five days of chemotherapy for each health state combination

		Delayed phase (days 2–5)		
		Complete protection	Complete response at best	Incomplete response
Acute phase (day 1)	Complete protection	4.5	3.7	1.7
	Complete response at best	4.3	3.5	1.5
	Incomplete response	3.8	3.0	1.0

Note: Determined by multiplying the number of days spent in each health state by the respective patient preference.

Table 5 – Health care resources and their cost in 2004 EUROs

Unit	Cost per unit (€)
Physician visits and hospitalisation	
General practitioner consultation[a]	35.48
Oncologist consultation[a]	42.67
Home visit[a]	50.51
Emergency room visit[b]	53.05
Hospitalisation (case mix)[c]	2760
Antiemetic prophylaxis	
Aprepitant (1 × 125 mg and 2 × 80 mg PO)	85.92
Ondansetron 8 mg (IV)	31.22
Dexamethasone (PO)[d]	
8 mg	1.71
12 mg	3.04
Rescue medication	
Average cost per medication[e]	14.30

a Einheitlicher Bewertungsmaßstab (EBM). Average charges for persons before and after retirement age.
b University hospital, personal communication.
c Weighted cost per case mix, using hospitalisation base rate of €2545, personal communication, Health insurance (Techniker Krankenkasse).
d Fortecortin was used to price dexamethasone.
e Based on German prices (Rote Liste) for alizapride, dimenhydrinate, domperidone, metoclopramide and ondansetron PO using different package sizes.

ences in the proportions of complete responders between the aprepitant and the control group in the acute and delayed phases of chemotherapy were simultaneously varied using simulation techniques, and 95% credibility intervals were generated.

To address uncertainties with utility values used in the model, scenario-based sensitivity analyses of the utility values from the literature were conducted. These analyses embrace utilities elicited with different techniques (VAS and TTO) as well as different correction factors across techniques.

To account for uncertainties with applying German cost data to healthcare resource utilisation data observed in the clinical trial, a series of one-way sensitivity analyses were performed for inpatient cost, outpatient cost, and cost of rescue medication. Each cost component was varied from low cost (70% of base case) to high cost (130% of base case).

3. Results

3.1. Health outcomes

Over an initial chemotherapy cycle, complete response was found in more patients in the aprepitant group (68%) than in the control group (48%). Figures for complete response cover the health states complete protection and complete response at best. More patients were projected to remain emesis-free (72% *versus* 49%) and CINV-free (29% *versus* 22%) with the aprepitant regimen than with the control regimen. The number of emetic events was approximately twice as high in patients on the control regimen. About 16% more patients in the aprepitant group were estimated to experience no impact on daily life due to CINV.

Based on our calculations over a single chemotherapy cycle, patients on aprepitant gained an additional 0.6 quality-adjusted life days (3.5 *versus* 2.9 in the control group). This

Table 6 – Health outcomes over a 5-day cycle

Outcomes	Aprepitant regimen	Control regimen	Absolute difference	% Change from control regimen
Emetic events per patient	1.63	3.07	(1.44)	–47
Average emesis-free days	4.4	3.7	0.7	19
Average CINV[a]-free days	2.1	1.8	0.3	17
Complete responders	67.5%	47.5%	20%	42
Emesis-free patients	71.8%	49.4%	22.4%	45
CINV-free patients	29.4%	21.6%	7.8%	36
No or minimal impact on daily life due to CINV	74.4%	63.9%	10.5%	16
Quality-adjusted life days	3.53	2.90	0.63	22
Quality-adjusted life years	0.0097	0.0080	0.0017	22

a Chemotherapy-induced nausea and vomiting.

Table 7 – Treatment cost per patient and cycle in 2004 Euros

Item	Aprepitant regimen (in €)	Control regimen (in €)	Difference (in €)
Antiemetic prophylaxis			
Aprepitant	85.92	0	85.92
Day 1	124.88	124.88	0
Ondansetron			
Dexamethasone			
Day 1	5.13	8.55	–3.42
Day 2–4	9.12	18.24	–9.12
Subtotal	225.05	151.67	73.38
Health-care resource utilisation per cycle			
Consultations (general practitioner, specialist, at home)	8.84	9.28	–0.44
Emergency room	2.12	2.33	–0.21
Hospitalisation	136.10	151.86	–15.76
Rescue medication	7.93	15.30	–7.37
Subtotal	154.99	178.77	–23.78
Total	380.04	330.44	49.60

Notes: (a) Total cost offset due to aprepitant is €85.92–49.60 = €36.32.
(b) Aprepitant drug cost offset is (€36.32/€85.92) × 100 = 42%.

corresponded to gaining an equivalent of 15 additional hours of perfect health during the 5-days observation period with the aprepitant-based regimen compared to the control regimen. Outcome data for both treatment groups are summarised in Table 6.

3.2. *Cost and cost-effectiveness*

Incremental drug cost per patient and cycle for antiemetic prophylaxis was €73.38 (Table 7). Expected health-care utilisation cost was €154.99 in the aprepitant group and €178.77 in the control group. Hence, it was estimated that 42% of the aprepitant drug cost was offset by lower resource use in the aprepitant group. Cost offsets arose mainly from lower doses of dexamethasone (€12.54), reduced use of rescue medication (€7.38), and avoided hospitalisations (€15.86).

The cost-effectiveness of aprepitant was estimated as incremental cost over incremental efficacy and was calculated at €28,891 per QALY (Table 8). Sensitivity analyses using different utility values show a range of €24,653 to €41,880 per QALY gained with aprepitant (Table 9). The lower and upper bound was based on different techniques to elicit utility values (VAS *versus* TTO) as published by Sun *et al.*[13] Referring to sensitivity analyses regarding costs, results were most sensitive to costs of hospitalisations and rescue medication, whereas the variation of outpatient costs only slightly impacted on the incremental cost-effectiveness ratios. The range was €26,135–31,646 per QALY gained with aprepitant (Table 10). Simulation-based sensitivity analyses over variability in the difference in proportions of patients experiencing complete response showed 95% of simulations resulted in cost per QALY gained with aprepitant between €16,172 and €52,694.

4. Discussion

The analysis of clinical trial data demonstrates an estimated absolute gain of 20% in terms of patients who responded completely when aprepitant is combined with ondansetron plus dexamethasone for prophylaxis of highly emetogenic chemotherapy. Complete response covered patients who nei-

Table 8 – Cost-effectiveness of aprepitant in Germany

Item	Aprepitant regimen	Control regimen	Difference	Incremental cost-effectiveness ratio
Quality-adjusted life years	0.0097	0.0080	0.0017	
Cost of antiemetic prophylaxis and health care resources utilised	€380.04	€330.44	€49.60	
Cost per quality-adjusted life year				€28,891

Table 9 – Utility values – scenario-based sensitivity analysis

Utility or CE result	Base case	Grunberg VAS	Grunberg VAS (1.18)[b]	Grunberg VAS (1.07)[b]	Sun VAS	Sun TTO
U (Complete Protection)	0.9	0.79	0.9322	0.8453	1	1
U (Com. Resp. at Best)[a]	0.7	0.602	0.7104	0.6441	0.7674	0.7674
U (Incomplete Response)	0.2	0.27	0.3186	0.2889	0.18	0.5
Cost per QALY Gained with EMEND	€28,891	€39,462	€ 33,442	€36,880	€24,653	€41,880

a Utilities for complete response at best state estimated using Borjeson *et al.* mild nausea utility of 0.7674 and renormalising.
b Multipliers for VAS utilities per citation in Grunberg article of O'Leary et al. plateau models. The 1.18 multiplier corresponds to 'cancer patient relative's responses' (utilised by Grunberg in his article) and the 1.07 multiplier corresponds to 'cancer patient responses'.

Table 10 – Costs – one-way sensitivity analyses

Cost parameter	Marginal cost per quality-adjusted life years (Euro)[a]	
	Low costs (70% of base case)	High costs (130% of base case)
Inpatient costs	€31,646	€26,135
Outpatient costs[b]	€29,005	€28,777
Rescue medication[c]	€30,180	€27,601

a Base case cost per quality-adjusted life year: €28,891.
b Outpatient costs include primary-care physician visits, laboratory visits, home health care, specialist visits, and emergency room visits.
c Rescue medication reflects rescue medications observed in phase III clinical trials.

ther experienced emesis nor required rescue therapy. The benefits of an aprepitant regimen also translated into a lower number of emetic events, a higher number of symptom-free days, and fewer patients who were impaired in their daily life due to CINV.

The ultimate goal of any medical intervention is to increase health-related quality of life and/or life expectancy. CINV is not a life-threatening condition but has a considerable impact on patients' quality of life[13,11] and belongs to the most distressing adverse effects of chemotherapy.[2] On a scale with 0.0 for death and 1.0 for perfect health, patients rate the presence of emesis and/or nausea as low as 0.2.[13] In particular, CINV that occurs during the 3-day period after chemotherapy, when the patient is at home, has a negative effect on a patient's ability to care for himself or herself. Patients may have difficulties preparing or eating meals, performing household tasks, or enjoying other daily activities.[14] The functional living index-emesis (FLIE) questionnaire showed that significantly more patients receiving aprepitant reported minimal or no impact on daily life compared with patients on standard therapy.[8,9] Furthermore, the experience of CINV may lead patients to postpone or withdraw from subsequent courses of chemotherapy, with negative effects on the management of their disease.[19] To that end an equivalent of an additional 15 h of perfect health during a 5-days observation period such as that provided by aprepitant in our study appears to be a major step toward greater feasibility and acceptance of the health benefits of modern chemotherapy. This 5-day outcome from a 5-day intervention can be put into perspective once QALYs gained from other interventions with similar duration and follow-up become available.

Cost-effectiveness analyses assess the incremental cost of an intervention versus its incremental benefits and are performed when one therapy has better efficacy but a higher acquisition cost than another. In assessments of 5-HT_3 receptor antagonists, both drug and non-drug healthcare resources play an important role.[20–24] Considering these, aprepitant was found to be cost-effective when combined with ondansetron plus dexamethasone in highly emetogenic outpatient chemotherapy (€28,891 per QALY). While a cost per QALY threshold has not been set in Germany yet, our estimate indicates that aprepitant provides good value for money, *e.g.* compared to incremental cost per QALY of £30,000 (€43,600 on 10th February 2005) suggested by the National Institute for Health and Clinical Excellence (NICE).[25] Our model may be on the conservative side, as we did not factor in manufacturer rebates and patient co-payments. Also, we did not consider reduced cancer morbidity and mortality due to better tolerability and feasibility of palliative and life-saving chemotherapies co-administered with aprepitant.

Cost offsets were calculated based on all observed healthcare resource utilisation, and some may reflect non-statistically significant differences between arms. All reported healthcare contacts in ambulatory or hospital visits are reflected in the analyses, as the trial data did not provide attribution of the relatedness of such healthcare to CINV. No attempt at an arbitrary post hoc differentiation of these events by the supposed underlying proximal cause of admission was made.

The ondansetron dosing regimen used in the clinical trials (32 mg IV on day 1) does not correspond exactly to practice in Germany, where the usual dose of ondansetron for CINV prophylaxis is 8 mg IV on day 1. However, clinical studies have shown that the efficacy of ondansetron at preventing CINV due to cisplatin- and non-cisplatin-based chemotherapy differs only marginally between doses of 8 mg IV and 32 mg IV.[26,27] We therefore assumed that the incremental efficacy observed in the clinical trials with aprepitant in combination with ondansetron 32 mg IV would also be seen with a lower dose of ondansetron. The incremental drug cost between the two regimens is not affected, being determined instead by lower doses of dexamethasone and the added cost of aprepitant.

On first glance one may assume that the different dosage of steroids in the aprepitant group and in the control group may have biased the results. But taking into account that aprepitant is a moderate inhibitor of the cytochrome CYP3A4 and therefore leads to an increased area under the curve for steroids[28], the smaller steroid dose applied in the experimental group was well justified and complies with current guidelines.

Although it was not documented in the studies whether patients were in a palliative or curative treatment setting which theoretically might bias the incidence of nausea and vomiting to a certain degree,[29] the two groups were balanced regarding well-defined and accepted risk factors of acute and delayed chemotherapy induced nausea and vomiting, *i.e.* age, gender, cisplatin-dosage, history of nausea and vomiting, alcohol consumption, and primary tumour diagnosis.[30] Moreover, a recent analysis revealed that the additional protection from nausea and vomiting by aprepitant was of the same magnitude for both genders.[31]

In a recent prospective observational study conducted in hospitals and office-based facilities in Germany shortly before the introduction of aprepitant, two out of three cancer patients (64%) still experienced CINV.[32] The incidence of delayed CINV (60.7%) was about twice as common as that of acute CINV (32.8%), underscoring the significance of improved prevention particularly of delayed CINV in Germany.

4.1. *Limitations*

There are limitations to the interpretation of these results. The calculations are based on clinical trial data rather than on randomised real-world effectiveness and cost data *versus* standard care. On the other hand, this bias, known as efficacy-effectiveness bias, may be small for highly symptomatic short-term therapies such as that studied here compared to long-term prophylaxis of asymptomatic chronic diseases.

We generalised outcomes of patients receiving cisplatin-based (cisplatin $\geqslant 70\ mg/m^2$) chemotherapy in the inpatient setting to outcomes of patients receiving highly emetogenic chemotherapy in the outpatient setting in Germany. These populations may differ in terms of cancer types, general health status and other important factors. On the other hand, cisplatin-based chemotherapy serves as a paradigm to chemotherapy of high emetic risk[33] and the trend toward outpatient chemotherapies in Germany will broaden the clinical spectrum of cancer patients seen in these institutions. CINV occurring within an inpatient stay does not necessarily accrue additional cost from third party payer perspective, except that it leads to a prolonged hospital stay. Referring to a German observational study, re-admission due to CINV can occur.[32]

The latest Multinational Association of Supportive Care in Cancer (MASCC) guidelines[34] recommend a combination of a NK1-receptor antagonist with a corticosteroid and a 5-HT_3 receptor antagonist in the acute phase (day 1) for prophylaxis of CINV induced by highly emetogenic chemotherapy. In delayed phase (days 2–5), a combination of a NK1-receptor antagonist and a corticosteroid is recommended. These regimens correspond to the aprepitant regimens used in the clinical trials. In the delayed phase (days 2–5), however, other than in the aprepitant trials, about 63% of patients in Germany received 5-HT_3 receptor antagonists in addition to metoclopramide plus a corticosteroid.[32,35] Two recently published meta-analyses of clinical trials both indicate that 5-HT_3 receptor antagonists given in the delayed phase in addition to corticosteroid or corticosteroid/metoclopramide do not improve the prevention of delayed CINV.[36,37] According to 2005 data of the Institute of Medical Statistics (IMS), German patients receive antiemetic treatment with 5-HT_3 receptor antagonists over a longer period than one day, *e.g.* patients with non-small-cell lung cancer receiving cisplatin-based chemotherapy are treated on average over 3 days with ondansetron i.v. and over 2.5 days with ondansetron oral.[38] Inclusion in the model of 5-HT_3 receptor antagonist use in the delayed phase for the control regimen results in the aprepitant-based regimen being even more cost-effective versus the control regimen.

Healthcare resource utilisation observed in multinational clinical trials can differ across countries and may not be reflective of healthcare resource use in real practice. The extent to which resource utilisation is associated with the trial per se rather than with usual practice is a well-known problem.[39] The presence of these 'protocol-driven' costs can lead to under- or overestimation of costs.

At present no real-world data on CINV prophylaxis in Germany are available. Therefore, calculations were based on pooled data from two randomised controlled trials carried through in another health system. Assessment of CINV prophylaxis associated health outcomes and resource use under routine care in Germany is an area of potential future research. Another important question that merits future study is whether there is an effect in terms of reduced cancer morbidity and mortality due to better tolerability and feasibility of palliative and life-saving chemotherapy.

5. Conclusion

As cancer chemotherapy has led to better medical outcomes, patients' concerns about quality of life and adverse effects have become increasingly important. Chemotherapeutic regimens have improved and are more precisely targeted than in the past, however, CINV remains a major obstacle and affects patients' satisfaction with treatment. Clinical data show that the aprepitant-based regimen for treatment of CINV results in better outcomes. It was estimated that the improved protection against CINV provided by the addition of aprepitant resulted in an equivalent of 15 additional hours of perfect health per cycle (0.63 quality-adjusted life days). In patients undergoing highly emetogenic outpatient chemotherapy at office-based facilities, use of aprepitant was found to be cost-effective from the perspective of statutory health insurance, with a considerable proportion of aprepitant cost being offset. Our results refer to the first chemotherapy cycle; however, we would expect to see similar results across multiple cycles given the favourable clinical results for the added cycles.

Conflict of interest statement

Florian Lordick: received a research grant and lecture honoraria from MSD Sharp & Dohme GmbH.

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James Pellissier: Is an employee of Merck research laboratories.

Glenn Davies: Is an employee of Merck research laboratories.

Robert Deuson: Was an employee of Merck research laboratories at the time of the writing of the manuscript.

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