Treatment cost development of patients undergoing remission induction chemotherapy: a pharmacoeconomic analysis before and after introduction of posaconazole prophylaxis

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Summary

Prior clinical trials have demonstrated efficacy and effectiveness of posaconazole in the prophylaxis of invasive fungal diseases in high-risk patients. Controversy exists about the cost-effectiveness of this approach. We performed an analysis comparing the direct costs of posaconazole prophylaxis against polyene mouthwash (thrush) prophylaxis in patients with acute myelogenous leukaemia (AML). Data of AML patients receiving remission-induction chemotherapy were extracted from the CoCo-Nut (Cologne Cohort of Neutropenic Patients) database to compare hospital costs of patients before (2003–2005) and after (2006–2008) introduction of posaconazole prophylaxis. Treatment on general ward, intensive care unit (ICU), mechanical ventilation, diagnostic procedures, and all anti-infectives were calculated. Patient groups were well matched according to age, gender and duration of neutropenia. The mean costs per patient in the posaconazole group (n = 76) and the polyene mouthwash group (n = 81) were €21 040 (95% confidence interval (CI): €18 204–€23 876) and €23 169 (95% CI: €19 402–€26 937) per patient. Antifungal treatment costs were €4580 (95% CI: €3678–€5482) and €4019 (95% CI: €2825–€5214). Duration on the ICU was 2582 (95% CI: 984.1–4181.7) and 5517 (95% CI: 2206–8827.3) min. In our hospital, primary antifungal prophylaxis by posaconazole was cost-effective. There was a trend towards cost savings, which was primarily caused by a shorter overall length of stay and the less frequent ICU treatment.

Keywords: Posaconazole, prophylaxis, costs, cost-effectiveness, pharmacoeconomic analysis, neutropenia.

Introduction

The incidence of invasive fungal diseases (IFDs) such as invasive pulmonary aspergillosis has increased in recent decades.1 Particularly patients with acute myelogenous leukaemia (AML) or myelodysplastic syndrome (MDS) undergoing first-remission induction chemotherapy are at high risk of contracting an IFD. These infections are associated with high morbidity and mortality rates.2 While early treatment seems to improve outcome,3 it is particularly difficult to establish the diagnosis of IFDs. Initiating treatment therefore often relies on surrogate markers, such as CT morphology and serological tests.4
In this scenario, broad-spectrum antifungal prophylaxis has become increasingly common, especially after clinical trials have demonstrated a reduction in the mortality of high-risk patients by use of this approach.\textsuperscript{5–7}

Posaconazole, a triazole broad-spectrum antifungal agent with activity against many clinically relevant pathogenic fungi, has been approved in Europe for the primary prophylaxis of IFDs in AML/MDS patients during neutropenia following remission-induction chemotherapy. It has received recommendations by all major German and international treatment guidelines.\textsuperscript{8–10} While clinical efficacy and effectiveness of posaconazole prophylaxis have been demonstrated,\textsuperscript{5, 11–13} its impact on the direct and indirect treatment costs remains unknown from the perspective of the German health system.

With the implementation of the Institute for Quality and Efficiency in Health Care (IQWIG) in Germany, cost-effectiveness evaluation of pharmaceuticals and medical interventions has been professionalised in the German health care system.\textsuperscript{14, 15} These evaluations describe the relation between the medical benefit and cost aspects of various therapy alternatives and can be a basis for future recommendations on drug approval and appropriate drug pricing.

In times of increasing budget restrictions, health economic evaluation is focused on a possible economic benefit in the treatment of diseases. Several studies exist describing the cost-effectiveness of antifungal prophylaxis. An earlier analysis performed in the Netherlands revealed mean medical costs per patient with AML or MDS of €57,750 (patients without invasive aspergillosis) to €83,300 (patients with probable or proven invasive aspergillosis).\textsuperscript{16} Comparable results were obtained by a German study, reporting direct costs for treatment of AML/MDS patients of €30,454 without and €51,517 with IFD.\textsuperscript{17} In another study, mean direct costs of a probable or proven IFD episode amounting to €51,033 per AML/MDS patient were observed.\textsuperscript{18} Current studies report posaconazole prophylaxis as being more cost-effective regarding direct costs as compared to other azoles in the prevention of IFDs in high-risk patients.\textsuperscript{19–21} However, data of international studies are inconclusive from the German health care perspective, given specific legal regulations, local drug pricing, discount agreements, reimbursement criteria and the complex mechanisms of the German health care system to compensate hospital expenses.

In this situation, we performed a comprehensive pharmacoeconomic evaluation of posaconazole compared to polyene mouthwash (thrush) prophylaxis.

**Materials and methods**

In the University Hospital of Cologne, posaconazole was introduced as standard of care in January 2006. Before the introduction of posaconazole, patients received oral mouthwash prophylaxis with a polyene antifungal. We performed a retrospective analysis of treatment costs during the 2006–2008 period (posaconazole) compared to historical data from 2003 to 2005 (topical polyene, i.e. oral nystatin or amphoteri-cin B mouthwash). An earlier analysis of the same patient groups had shown superior effectiveness of the posaconazole prophylaxis compared to polyene mouthwash prophylaxis.\textsuperscript{11}

To explore the economic impact of primary antifungal prophylaxis with posaconazole, we performed a health economic evaluation of direct treatment costs of patients treated before and after introduction of posaconazole as standard of care. The analysis was performed from the perspective of the German health care system. All data items were documented in the database of the Cologne Cohort of Neutropenic patients, CoCoNut (System AG, Lohmar, Germany). This prospective cohort was established in 1995 with the aim of a comprehensive data collection of all patients developing neutropenia after receiving chemotherapy for any kind of malignant disease, treated in the University Hospital of Cologne.

**Patients**

The study was performed in the Department I of Internal Medicine, University Hospital of Cologne, Germany, one of the major providers of Hematology and Oncology services in Germany. All patients with AML treated by the department receiving remission-induction chemotherapy during the period from January 2003 until December 2008 were eligible for the study. Patient exclusion criteria were (i) patients receiving systemically active antifungal treatment for suspected or proven invasive fungal disease prior to chemotherapy; (ii) patients receiving systemically active antifungal prophylaxis other than oral posaconazole; (iii) patients receiving posaconazole before January 2006 as part of clinical trials. There was no age limit for inclusion and no patient was included twice. The following induction chemotherapy regimens, adopted from the AML Cooperative Group (AML-CG), were applied: high-dose cytarabine and mitoxantrone (HAM), 6-thioguanine, cytarabine and daunorubicin (TAD), or sequential high-dose cytarabine and idarubicin or mitoxantrone (S-HAI and S-HAM).
Patients were categorised into two groups: patients treated between January 2003 and December 2005 receiving topical polyenes as oral solution or tablets as standard of care (polyene mouthwash group) and patients treated between January 2006 and December 2008 receiving oral posaconazole 200 mg three times daily (posaconazole group). Diagnostic, therapeutic and hygienic standards remained unchanged during the study period. A special neutropenic diet was replaced by standard diet for all haematological patients in January 2008. Construction was ongoing around the hospital for the whole observational period; however, the patient wards were not directly affected or otherwise changed.

Costs

Direct treatment costs were calculated by applying accounting factors to selected variables at least possibly connected with infectious complications (Table 1).

Costs of an inpatient stay on the general ward were obtained from published records using the German Diagnosis Related Groups (G-DRG)-Report browser. Each case was calculated by the year of treatment and the used G-DRG (i.e. R60A, R60B, R60C, R04A, R63B; see Table 2 for details on the different G-DRG codes), to control for annual variations. The overall costs for each G-DRG are structured in various types of costs. To prevent double counting of drug costs, we excluded pharmacy costs (listed in the cost profiles under 4a and 4b in the G-DRG-Report browser) from our evaluation. The included cost components were as follows: (i) staff costs: medical, nursing and technical service, (ii) material costs: other medical requirement, (iii) staff and material costs: medical and non-medical infrastructure. The costs for the cytostatic agents were not included in the cost calculation of general ward treatment, as these are expensive drugs without direct connection to infectious events; to the contrary, fungal infections causing a delay or cessation of anti-cancer chemotherapy could cause a bias towards cost reduction by fungal infections. Costs of intensive care unit (ICU) stay (for any reason) and mechanical ventilation were calculated based on published data. The patient-customised staff and material costs for the intensive care and the mechanical treatment were as follows: (i) medical, nursing and technical service, (ii) drugs, (iii) blood equipment (i.e. one-way material). The non-patient-customised staff and material costs were as follows: (i) medical infrastructure (i.e. pharmacy, nursing direction, ambulance service), (ii) non-medical infrastructure (i.e. energy, technology, management). Daily costs of all anti-infectives were calculated by the WEB-APO® LAUER-Taxe, Fürth, Germany. This database offers comprehensive pharmaceutical information, including annual vendor information, annual tax determination and annual price development of pharmacy purchase prices in Germany. If several vendors were possible to use, the lowest price of the cheapest

Table 1 Direct treatment cost parameters.

| Length of stay on general ward | Unit cost ($) |
|-------------------------------|--------------|
| Length of stay on intensive care unit (ICU) | 260.46 |
| Mechanical ventilation | 256.90 |
| Acquisition cost of anti-infectives (antivirals, antifungals, antibacterials) | 236.03 |
| Diagnostic measures, i.e. number of computed tomography (CT) scans and blood cultures, bronchoalveolar lavage (BAL) samples and serological tests | 158.64 |
| Duration on the ICU | 477.10 |
| Duration of general ward (R63B) Day (e.g. 2008) | 1145.00 |
| Duration of mechanical ventilation | 11.71 |
| CT scan 1 test | 241.31 |
| Blood culture 1 test (one culture) | 10.90 |
| BAL 1 test | 120.66 |
| Serological sample 1 test | 8.05 |
| Posaconazole Daily dose (e.g. 2008) | 100.32 |
| Amphotericin B (mouthwash) Daily dose (e.g. 2005) | 2.72 |

BAL = Bronchoalveolar lavage; CT = Computed tomography; ICU = Intensive care unit.

Table 2 Resource costs.

| Item | Unit | Unit cost ($) |
|------|------|--------------|
| Duration on general ward (R60A) Day (e.g. 2008) | 260.46 |
| Duration on general ward (R60B) Day (e.g. 2008) | 256.90 |
| Duration on general ward (R60C) Day (e.g. 2008) | 236.03 |
| Duration on general ward (R04A) Day (e.g. 2005) | 158.64 |
| Duration on general ward (R63B) Day (e.g. 2008) | 477.10 |
| Duration on the ICU Day | 1145.00 |
| Duration of mechanical ventilation Hour | 11.71 |
| CT scan 1 test | 241.31 |
| Blood culture 1 test (one culture) | 10.90 |
| BAL 1 test | 120.66 |
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| Amphotericin B (mouthwash) Daily dose (e.g. 2005) | 2.72 |

BAL = Bronchoalveolar lavage; CT = Computed tomography; ICU = Intensive care unit.

Definitions of the G-DRG: R60A = Acute myeloid leukaemia with highly complex chemotherapy; R60B = Acute myeloid leukaemia with intensive chemotherapy, dialysis or with complicating diagnosis or port implantation; R60C = Acute myeloid leukaemia with intensive chemotherapy, with extremely severe complications and/or comorbidities (cc) or complex diagnosis of leukaemia or chemotherapy with moderately complex with complicating diagnosis or dialysis or port implantation or with extremely severe cc with complex diagnosis of leukaemia; R04A = Other haematological and solid tumours with established procedure, with very severe or severe cc; R63B = Other acute leukaemia with intensive chemotherapy, dialysis or with sepsis or with agranulocytosis or port implantation, age <6 years or with extremely severe cc (G-DRG-System, http://g-drg.de, last accessed 2012-07-11).
vendor was used for the relevant unit cost. Regarding medication doses, patients were assumed to have an average body weight of 75 kg. Due to often incomplete dose documentation, standard daily doses of anti-infectives were determined by infectious disease specialists (JJV, OAC) based on local treatment guidelines. Like the costs of the general ward treatment, the costs for all anti-infectives were calculated based on current prices at the time of drug dispense. Costs of all diagnostic measures were calculated, based on the German ‘Gebührenordnung der Ärzte’ (medical fee schedule, GoÄ). The GoÄ serves as calculation base of medical services, e.g. serological tests, blood cultures and Bronchoalveolar lavages taken and CT scans performed. Table 2 presents the resource costs as basis of our health economic evaluation.

Data documentation

The observational periods started with the date of hospitalisation and ended with the date of discharge. We included the following data-items into the documentation: age, gender, ethnicity, underlying disease, status of underlying disease, size, weight, chemotherapy protocol, date of admission and discharge, first day and last day of chemotherapy, chemotherapy cycle number, transfer to the ICU for any reason, length of stay on the ICU for any reason, reason of transfer on the ICU, mechanical ventilation, radiation, HIV status, bone marrow transplantation, central venous catheters, microbiological/serological/virological results, pulmonary CT scans, incidence of skin infiltrate, abscesses, start date/end date/means of administration and indication of all anti-infectives, granulocyte-colony stimulating factors (G-CSF) and relevant interacting medication, leukocyte/neutrophil counts, days with diarrhoea and last but not least highest daily temperature. Patient Clinical Complexity Level (PCCL) and German Procedure Classification (OPS) for chemotherapeutic regimens were extracted from the hospital information system.

All patient data were documented by trained medical staff, i.e. medical documentalist.

Cost calculation and statistical analysis

Costs were derived by factoring the above-mentioned data items and cost scales. All costs are presented in euros (€). Overhead costs for nonclinical support services, e.g. maintenance, hospital administration, rent and leasing, carriers, monitors, or air conditioning were not included in cost calculation. Cost for energy was only calculated for the treatment on the ICU for any reason, based on published data. Discounting could not be analysed due to non-disclosure agreements, and no adjustments were made for inflation. Statistical analyses were performed using IBM SPSS Statistics, for Windows version 19.0 (IBM Corp., Armonk, NY, USA) and version 20.0 (IBM Corp.). Primary endpoint was the overall treatment cost. Other cost results were tested as exploratory outcome parameters. Student’s t test was used to compare normally distributed, continuous variables between the two groups. The level of significance was defined as \( P < 0.05 \). A 95% confidence interval (95% CI) was also calculated for each cost parameter. Furthermore, patient and cost data are presented as median, mean, and/or range, as appropriate.

Results

During the observational period, a total of 167 patients received induction chemotherapy for treatment of AML. Eight of these were excluded for receiving posaconazole as part of a clinical trial before 2006. Two patients, one of the posaconazole group and one of the polyene mouthwash group could not be included into the analysis as the patient file was incomplete. Taken together, 157 patients had complete data sets and were eligible for health economic evaluation. Eighty-one patients received polyene mouthwash prophylaxis (polyene mouthwash group) while 76 patients received systemic posaconazole prophylaxis (posaconazole group). All patients were Caucasian from Europe and the Near East.

Patient characteristics

Characteristics of the study population are summarised in Table 3. Groups were well matched by age and gender. While there was a significant difference in G-DRG coding between groups, PCCL and OPS for chemotherapeutic regimens did not differ between groups (Table 3). There was only one significant difference with respect to serological samples taken.

Drug administration outcome

Table 4 shows statistics of anti-infective use in both treatment groups. In the posaconazole group, significantly less daily doses of antifungals and carbapenemes (excluding prophylaxis) were used and patients had significantly less days on treatment with systemically active antifungals.
The mean overall direct treatment costs per patient were €21,040 in the posaconazole group and €23,169 in the polyene mouthwash group, resulting in savings of €2,129 per patient receiving posaconazole. Major cost savings were caused by a shorter overall length of stay (43.5 vs. 48 days) and a shorter ICU treatment for any reason (43 vs. 92 h). The overall treatment costs on the general ward were the most important cost driver, with 55.4% and 48.6%, respectively, of the overall costs. Anti-infective drug use (28.8% and 24.7%) and the treatment on the ICU for any reason (10.8% and 21.0%) were next. Due to the high overlap observed between the 95% confidence intervals for the costs in both groups, only the costs for serological samples taken were significantly different. Table 5 presents an overview of all cost parameters and their respective percentage of overall costs for both groups. The differences between cost factors of both groups are demonstrated in Fig. 1.

Discussion

The introduction of innovative, yet expensive new drugs in the field of antifungal prophylaxis has raised concern regarding their impact on hospital budgets in an increasingly pressurised health system. We performed a pharmacoeconomic evaluation of posaconazole prophylaxis in AML patients to weigh potential financial benefits of preventing IFDs, thus reducing patient morbidity and mortality, against the cost of the antifungal. Our analysis revealed comparable treatment costs in both treatment groups; there was a trend towards modest cost savings of €2,129 by posaconazole prophylaxis. This result is especially noteworthy for the field of haematology, where most new (and expensive) pharmaceuticals are associated with an increase in overall costs of treatment.

In our observation, the expenses of the prophylaxis were outweighed by reduced patient morbidity, allowing shorter hospitalisation, less ICU treatment for any reason and less need for the most expensive antibacterials. Especially inpatient hospital days and treatment on the ICU are known to belong to the most important cost drivers in health economic evaluations. While there is a general trend towards a reduced length of stay following introduction of the G-DRG system, this has not been true for patients with haematological or oncological malignancies. Especially for patients with AML or MDS, a marginal increase in the average length of stay has been reported. The results of this study are consistent with two cost-effectiveness analyses of posaconazole prophylaxis compared to fluconazole or itraconazole conducted from the Canadian and the Swiss health care perspective. The revealed savings of direct costs were Can...
Table 4 Drug administration outcome.

| Item                                      | Posaconazole group (n = 76) Mean (95% CI) | Polyene mouthwash group (n = 81) Mean (95% CI) | P*  |
|-------------------------------------------|-------------------------------------------|-----------------------------------------------|-----|
| Daily doses of (excluding prophylaxis)    |                                            |                                               |     |
| Antifungals                               | 7.7 (5.04–10.33)                          | 13.9 (10.46–17.32)                           | 0.005 |
| Piperacillin                               | 8.1 (6.09–10.07)                          | 6.4 (4.88–7.96)                              | 0.187 |
| Carbenepenems                              | 6.6 (4.76–8.53)                           | 10.1 (7.85–12.25)                           | 0.021 |
| Glycopeptides                              | 5.7 (4.00–7.42)                           | 5.1 (3.46–6.64)                              | 0.573 |
| Cephalosporines                            | 5.1 (3.48–6.65)                           | 4.8 (3.16–6.44)                              | 0.819 |
| Fluoroquinolones                           | 4.3 (2.58–6.05)                           | 5.0 (3.24–6.81)                              | 0.572 |
| Days on treatment with (excluding prophylaxis) |                                        |                                               |     |
| Systemically active antifungals           | 8.3 (5.65–11.01)                          | 13.9 (10.48–17.30)                           | 0.012 |
| Antibacterials                             | 21.5 (18.82–24.11)                        | 22 (19.34–24.57)                             | 0.794 |
| Days until treatment with                 |                                            |                                               |     |
| Systemically active antifungals           | 4.9 (2.79–7.07)                           | 4.8 (3.20–6.43)                              | 0.929 |
| Antibacterials                             | 2.4 (1.44–3.43)                           | 2.5 (1.63–3.44)                              | 0.886 |

CI = Confidence interval.
* t-test for independent groups (two-sided).

Every significant P-value in Table 4 is marked in bold.

Table 5 Overview cost distribution.

| Cost Parameter (£) Mean (95% CI) | Posaconazole group (n = 76) % of overall costs | Polyene mouthwash group (n = 81) % of overall costs | P*  |
|----------------------------------|-----------------------------------------------|----------------------------------------------------|-----|
| Antifungals                      | 4580 (3678–5482)                             | 21.8                                               | 17.3 0.457 |
| Antibacterials                   | 1316 (1039–1593)                             | 6.3                                               | 6.6 0.289 |
| Diagnostics                      | 159 (57–261)                                 | <1.0                                              | 165 (75–254) 0.931 |
| CT scans                         | 611 (478–744)                                | 3.0                                               | 653 (552–754) 0.619 |
| Blood cultures                   | 349 (251–448)                                | 1.7                                               | 366 (291–442) 0.784 |
| Serological samples              | 86 (73–99)                                   | <1.0                                              | 88 (76–100) 0.887 |
| BALs                             | 80 (69–92)                                   | <1.0                                              | 114 (98–130) 0.001 |
| ICU treatment                    | 2273 (866–3679)                              | 10.8                                              | 4855 (1941–7768) 0.115 |
| Mechanical ventilation           | 294 (47–541)                                 | 1.4                                               | 242 (1–483) 0.763 |
| General ward treatment           | 11 652 (10 540–12 764)                       | 55.4                                              | 11 253 (10 226–12 279) 0.600 |
| Overall costs                    | 21 040 (18 204–23 876)                       | 100                                               | 23 169 (19 402–26 937) 0.375 |

BALs = Bronchoalveolar lavages; CI = Confidence interval; CT = Computed tomography; ICU = Intensive care unit.
* t-test for independent groups (two-sided).

Every significant P-value in Table 5 is marked in bold.

Figure 1 (tornado diagram) Percentage cost savings (to the left of the vertical axis) or additional expenditure by posaconazole prophylaxis.
Another pharmacoeconomic evaluation showed savings of direct costs of posaconazole prophylaxis compared to voriconazole prophylaxis amounting to AU$ 17 458 per patient.\textsuperscript{12} A controlled trial of posaconazole vs. fluconazole imaging findings in N Engl J Med 2011; 326: 97–106. Also, new subgroups for coding an AML were defined during the study period.\textsuperscript{14–16} Also, new subgroups for coding an AML were defined during the study period.\textsuperscript{14–16} Another issue is the high prevalence of discounting in contracts between pharmaceutical companies and hospital pharmacies. The details of such contracts are often well-kept secrets, thus rendering exact calculations of real-life drug prices all but impossible. Given the moderate number of cases, we saw considerable overlap of confidence intervals between both groups. The current health economic evaluation considered only direct treatment costs, although incremental and indirect costs are of high significance from a societal point of view.\textsuperscript{17,18,37,38} Also, being a non-interventional study based on chart review, it cannot be ruled out that unobserved changes occurred in fungal epidemiology or customary treatment practice between the observational periods.

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Conflict of Interest

S.M.H. has received research grants from Merck and Pfizer. O.A.C. is supported by the German Federal Ministry of Research and Education (BMBF grant 01KN1106), has received research grants from Actelion, Astellas, Basilea, Buyer, Biocryst, Celgene, F2G, Genzyme, Gilead, Merck/Schering, Miltenyi, Optimer, Pfizer, Quintiles and Viropharma, is a consultant to Astellas, Basilea, F2G, Gilead, Merck/Schering, Optimer, and Pfizer, and received lecture honoraria from Astellas, Gilead, Merck/Schering, and Pfizer. J.J.V. has received research grants from Astellas, Infectopharm, Pfizer and Merck/Schering, and has served on the speakers’ bureau of Merck/Schering, and Pfizer. M.J.G.T.V. has been a speaker for Astellas Pharma, Gilead Sciences, Merck/MSD and Pfizer. She has received research grants from 3M.

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