Health resource consumption and costs attributable to chemotherapy-induced toxicity in German routine hospital care in lymphoproliferative disorder and NSCLC patients


1Department of Hospital Pharmacy; 2Third Medical Department, Klinikum rechts der Isar, Technische Universität München, Munich; 3Department of Internal Medicine III, Klinikum Freising, Freising; 4Department of Transfusion Medicine and Haemostaseology, Klinikum der Universität München, Munich; 5Health Economics and Outcomes Research, IMS Health GmbH, Munich; 6Department of Gynaecology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

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Background: Multidrug chemotherapy (CT) is still associated with relevant side-effects. We assessed, under current practice patterns, frequency and severity of CT-induced toxicity and its economic consequences.

Patients and methods: Prospective, multicentre, longitudinal, observational cohort study with lymphoproliferative disorder (LPD) and non-small-cell lung cancer (NSCLC) patients, receiving first- or second-line (immuno-) CT (excluding myeloablative CT). Data were collected from patient interviews and preplanned chart reviews. Costs in 2007 euros are presented from the provider perspective.

Results: Two hundred and seventy-three patients (n = 153 LPD; n = 120 NSCLC) undergoing a total of 1004 CT cycles were assessable (age ≥ 65 years, 40%; female, 36%; Eastern Cooperative Oncology Group performance status ≥2, 11%; tumour stage ≥III, 56%; history of comorbidity, 80%). Fifty percent of cycles were associated with grade 3/4 toxicity and 37% (n = 371) with at least one hospital stay (outpatient/day care n = 154; intensive care n = 19). Mean (median) toxicity-related costs amounted to €1032 (€86) per cycle. Costs rose exponentially with the number of grade 3/4 adverse drug reactions (ADRs) and were highest in cycles affected by more than four ADRs, €10,881 (€5455); in cycles with intensive care, €14,121 (€8833); and in cycles affected by grade 3/4 infections and febrile neutropenia/leukopenia, €7093 (€4531) and €5170 (€2899), respectively. Five percent of CT cycles accounted for 56% of total expenses.

Conclusions: Individualised supportive care strategies are needed. Future research should focus on identifying toxicity clusters and patient characteristics predictive for high costs.

Key words: combined antineoplastic treatment protocols/adverse effects, costs and cost analysis, health resources, neoplasms/drug therapy

Introduction

Despite the progress of supportive care medicine over the past decades, multidrug chemotherapy (CT) is still associated with a broad range of adverse drug reactions (ADRs). However, little is known about the frequency and severity of CT-induced toxicity in clinical practice [1–4]. To establish cost-effective CT treatments with an improved toxicity profile, real-world data are necessary to determine treatment patterns, frequency and severity of side-effects and associated cost [2, 5]. Aside from the clinical consequences, i.e. necessary dose reductions [6], life-threatening complications [7] and impingement on patients’ quality of life [8], toxicity management has considerable economic impact, particularly in the inpatient setting [9, 10].

For European health care systems and especially for Germany, microeconomic data on supportive care interventions are scarce [11, 12]. The existing health economic literature, mainly studies from the United States, focuses on particular toxic effects such as anaemia [11, 13], febrile neutropenia (FN) [7, 14, 15], thrombocytopenia and bleeding [16, 17], mucositis [18] and CT-induced nausea and vomiting [2]. However, information on the cumulative cost of toxicity management, e.g. per treatment cycle, is not available.

In an environment of flat-rate reimbursement and high pressure on health care budgets, clinicians and policy makers need to understand the global impact of toxicity management on costs, not only to optimise current supportive care strategies...
but also to use more effective and less toxic CTs. In this
case, real-world data can serve as cost estimates in health
economic modelling [19]. Moreover, knowledge of the actual
cost of supportive care permits comparison with flat-rate
reimbursement, which is not necessarily fully cost covering [9, 20].

Also, the heterogeneity of (haemato) toxicity has been
studied widely in the past decade [7, 21]. Individualised
approaches to allocate expensive preventive measures seem
necessary to optimise supportive care strategies in the future.
For patient subgroups with high toxicity treatment cost,
prophylaxis is presumably very cost effective. Therefore,
identifying and characterising these patients seems important.

As a result, we prospectively assessed, under current practice
patterns, the occurrence of CT-induced toxicity and its impact
on health resource utilisation and costs. Our second goal was to
identify patient subgroups with high costs attributable to toxicity
management. As supportive care issues are especially large in
non-small-cell lung cancer (NSCLC) and lymphoproliferative
disorder (LPD) patients receiving several cycles of multidrug
(immuno-) CT [22, 23], consecutive recruitment was restricted
to this group of patients.

**patients and methods**

**study design and patient selection**

This prospective, longitudinal, multicentre observational cohort study was
conducted from January 2005 to June 2007 in two university and two
regular care hospitals in Germany. Centres were required to be experienced
in the administration of CT, including the prevention and management of
CT-induced complications, and to operate at all levels of current hospital
care.

Patients were eligible if they were assigned to first- or second-line
(immuno-) CT for NSCLC or LPD [non-Hodgkin’s lymphoma, Hodgkin’s
lymphoma, multiple myeloma, chronic lymphocytic leukaemia (CLL)].
Patients were enrolled consecutively; recurrent enrolment was possible. The
observation period was the length of one CT line (see following for
definition).

To avoid inclusion of patients whose CT was only initiated at study site,
but continued elsewhere, patients had to be scheduled for at least two CT
visits. Patients receiving myeloablative CT with stem cell support were
excluded, as were those who were not able to participate in patient
interviews due to linguistic or cognitive reasons.

Written informed consent was obtained from all patients; the study was
approved by the ethics committees of Technische Universität München
and Ludwig-Maximilians-Universität München.

Medical and economic data were collected from preplanned
comprehensive chart reviews and patient interviews. Chart data were
abstracted by trained staff of the hospital pharmacy of Klinikum rechts der
Isar. Data collection was standardised using a data manual.

One hospital CT visit was defined as CT application on
± 1 consecutive
days, followed by a ≥7-day CT-free interval. The length of one CT cycle as
well as the number of CT visits per cycle varied according to CT regimen.
One CT line was defined as the period from the start to the scheduled end
or discontinuation due to tumour progression or toxicity.

**patient characteristics**

Patient baseline characteristics extracted from medical charts included the
following: demographics, clinical history and comorbidity, cancer diagnosis
and CT regimen.

Comorbidities of heart, lung, pancreas, liver and kidney and
thromboembolic events as well as Eastern Cooperative Oncology Group
(ECOG) performance were analysed to indicate patients overall health
status at enrolment.

Tumour stage was classified using the TNM (tumour–node–metastasis)
and Mountain classification for NSCLC, the Ann Arbor system for
non-Hodgkin’s lymphoma and Hodgkin’s disease, and the Durie–Salmon
staging system for multiple myeloma. CLL stage was described according
to Rai. Therefore, Binet stage A was transformed to Rai stage 0. None of
the CLL patients had tumour stage higher than Binet A.

**evaluation of toxicity**

Occurrence and severity of CT-induced toxicity were recorded at each CT
visit or by telephone after the final CT visit according to the National
Cancer Institute—Common Terminology Criteria for Adverse Events
(NCI–CTCAE) version 3.0 and the causality criteria of the World Health
Organisation (WHO) Uppsala Monitoring Centre [24]. Frequency of toxic
effects was aggregated per treatment cycle. Toxic effects were surveyed using a
structured interview form.

In case of fever, outpatients were advised to undergo assessment of
haematological counts at least on a weekly basis. If blood cell count nadir
monitoring was provided by external institutions, a written request to
disclose blood cell count nadirs was transmitted via the patient.

FN was incorporated into the analysis as a composed variable. FN was
defined as fever ≥38°C and an absolute neutrophil count (ANC) <1x 10^9/l.
If ANC nadir was unavailable, febrile leukopenia (FL) was assessed
(leukocyte count <2x 10^9/l and fever ≥38°C).

**causality rating.** Only ADRs according to WHO causality rating (i.e. clinical
events with a reasonable temporal relationship to administration of the
drug) were considered for analysis [24].

**resource utilisation and costs**

Health care consumption due to toxicity was structured as follows:

- use of prophylactic or rescue supportive drugs (e.g. antiemetics,
colony-stimulating factors, antibiotics, antifungal drugs)
- use of red blood cell, platelet and plasma transfusions
- medical procedures, laboratory tests, chest X-rays or other diagnostic
  procedures
- number of treatment days for outpatient (ambulatory and daytime
  clinic) visits (e.g. for blood transfusion), hospitalisation (inpatient
  overnight admission) or extended hospitalisation (e.g. hospitalisation
due to fever); the term ‘hospital visit’ refers to both outpatient visits and
  inpatient admissions.

Hospitalisation was considered as extended when the patient was not
discharged the day after the last application of (immuno-) CT. With the
exception of CT visits postponed because of toxicity, preplanned hospital
visits for the purpose of CT administration were not considered; nor were
CT agents or health care consumption directly related to CT-induced
toxicity (e.g. cancer diagnostics, radiation therapy, surgery).

**costs.** Cost analysis was conducted from the hospital provider perspective.
Estimates of costs were reported as the quantity of different resources
consumed. The overall toxicity management cost per treatment cycle
(TM–TC) comprised the following:

- (Prolonged) hospitalisation, outpatient visits due to toxicity; cost of
  hospitalisation; cost of drugs, medical treatment and diagnostic
  procedures associated with toxicity management were added on top
- Hospital visits for CT application; only cost of drugs, medical treatment
  and diagnostic procedures associated with toxicity management; cost of
  hospitalisation was considered CT associated and therefore not included
  in the analysis.
All costs were calculated in 2007 euros and not discounted. Unit costs and sources of unit costs are shown in Table 1.

**statistical analysis**

Distribution of resource utilisation was described as the frequency or number of utilised services per treatment cycle, separated by type of service. Descriptive statistics [mean, median, standard deviation (SD) and 95% confidence intervals (CIs)] were carried out for costs and other continuous variables. Categorical variables were given with relative frequencies. The *t*-test for two independent samples or chi-square test was used for explorative two-group comparisons. Any *P* values given are two-sided. Data were analysed using Microsoft Excel™ 2003 or SAS 8.2 (SAS Institute Inc., Carry, NC).

One-way sensitivity analysis was carried out by varying cost factors of TMC-TC within the lower and upper limit of their 95% CIs. Moreover, to account for uncertainties caused by applying local cost data (Table 1) to health care resource utilisation data, main cost factors were varied by percentages [25, 26]: drugs (±25%) and hospital basic services (+12%; −8%), based on difference between the mean hospital daily cost in Bavaria and in German federal states with minimal and maximal daily hospital cost values in 2007 [27].

**results**

**patient baseline characteristics**

A total of 386 consecutively scheduled CT lines at four study sites were identified according to selection criteria. In 79% (*n* = 304), patients agreed to participate in the study. Eighteen CT lines had to be excluded from the analysis due to protocol violation, withdrawn informed consent or nonavailability of the patient chart. Overall, 286 CT lines (74%) were evaluable, with a total of 1004 CT cycles corresponding to 1531 CT visits. Thirteen patients were enrolled twice. Hence, the total number of patients was 273. Disposition of study patients is shown in Figure 1. The 99 non-participants and excluded patients were significantly older (63.9 versus 60.3 years, *P* = 0.016) and had higher ECOG performance status (ECOG ≥2: 28.3% versus 11%, *P* < 0.001) compared with the participants. Sex and cancer type were equally distributed (data not shown).

Of the 273 assessable patients, 120 (44%) had NSCLC and 153 (56%) LPD, with 98 of them being non-Hodgkin’s lymphoma. A diagnosis of Hodgkin’s lymphoma (*n* = 21), multiple myeloma (*n* = 26) and CLL (*n* = 8) was less frequent. Mean patient age was 60.3 years (SD 13.0); 40.3% of patients were at least 65 years old. At first enrolment, 56% of patients had stage >III disease and 11% an ECOG performance status of two or more; 80% of patients had a history of comorbidity. Most frequent comorbidities were heart disease (46.5%), an antecedent of thromboembolic episodes (18.7%) and pulmonary disease (16.5%).

NSCLC patients were significantly older than LPD patients and presented more often with stage III/IV disease, ECOG performance status of two or more, and comorbidities of the heart, lung and thromboembolic events (Table 2).

In 76% of CT lines, patients underwent first-line treatment. Twenty-one percent had previously received CT. Seven percent received radiation therapy within 6 weeks before CT and 11% a concomitant radio-CT. Forty-seven percent of CT lines for LPD were CHOP (combination CT with cyclophosphamide, doxorubicin, vincristine and prednisone)-like regimens and 78% of NSCLC lines platinum based. Predisposition to infection due to the presence of central venous catheters or port systems was documented in 22.4% of CT lines.

Mean cycle number per CT line was 3.5. Fifty-eight percent of CT lines for NSCLC and 13% for LPD were not completed as scheduled. The main reason for discontinuation of CT was tumour progression for NSCLC (52%) and toxicity for LPD (45%; Table 3).

![Figure 1. Study flow chart.](image-url)
occurrence of ADRs

The frequency of severe and potentially life-threatening toxic effects (i.e. NCI-CTCAE grades 3 and 4) is summarised in Table 4. Five hundred and two of 1004 CT cycles (50%) were associated with at least one episode of grade 3/4 ADR. Grade 4 ADRs were reported in 146 cycles (14.5%). Most frequent toxicity was leukopenia/neutropenia (grade 3/4: 27%; grade 4: 11.8%). Fatigue/asthenia/lethargy and oedema were found in 12.5% and 8.4% of cycles, respectively. Both grade 3/4 elevation of serum creatinine and infections were reported in 53 (5.3%) and 81 cycles (8.1%), respectively. FN/FL and grade 3/4 toxicity were reported in 371 of 1004 cycles (37%). Table 5 and Figure 2. Additional hospital visits due to toxicity were reported in 19 cycles (1.9%). Haemodialysis was carried out in two cycles.

consumption of health care resources

Toxicity-associated utilisation of health resources is shown in Table 5 and Figure 2. Additional hospital visits due to CT-induced toxicity were reported in 371 of 1004 cycles (37%). Inpatient toxicity management was more frequent than outpatient management (25.7% versus 15.4%). In 15.8% of cycles, CT visits were prolonged due to toxicity for a mean duration of 6.5 days. Rehospitalisation due to toxicity was observed in 13% of cycles (mean length of stay: 11.4 days). In 19 cycles (1.9%), an intensive care unit (ICU) stay was necessary.

Toxicity-associated use of drugs (prophylactic and rescue medication) was reported in 961 treatment cycles. Most frequently used drugs were aminoglycosides (95.4%). Antibiotics and/or antifungal drugs were given in 14% and granulocyte colony-stimulating factor support in 5.6% of CT cycles. Blood products including red blood cells, platelets, fresh frozen plasma, albumin and antithrombin III were reported in 27.5% of cycles. Other medical procedures, e.g. haemodialysis, implantation of central venous catheters due to phlebitis, monitoring for infusion reaction and glucocorticoid-induced hyperglycaemia, as well as consultations were necessary in 24.5% of cycles. The most relevant diagnostic procedure was microbiology testing (16%). Imaging and other diagnostic procedures (e.g. echocardiography, pulmonary function) were reported in 13% of cycles.

costs of toxicity management

The average costs per treatment cycle from the perspective of the provider (hospital) are presented in Figure 3. Mean (median) TMC-TC totalled €1032 (£86; 95% CI £835–1230), with €764 for hospital basic services including staff, which accounted for 74% of total cost, followed by costs for drugs, diagnostics and blood products (€128, £61 and £57), which accounted for 12%, 6% and 6%, respectively. Costs for (par)enteral nutrition and other medical procedures were £61 and £15 (£11), respectively, per CT cycle.

Although not significant, mean TMC-TC was slightly higher for NSCLC than for LPD patients (€1137 versus €967, respectively). This is mainly due to the higher cost for hospital basic services and staff.
More than half of CT cycles involved costs ≤€100, another 42% of cycles had toxicity-associated costs ranging from €101 to 5000. The remaining 5% of cycles (n = 53) had high costs (‡€5000) and generated 56% of total expenses in the observed cohort (Figure 4).

**subgroup analysis**

Subgroup analysis revealed that mean (median) costs are particularly high in cycles involving an ICU stay: €14 121 (€8833; 95% CI €8401–19 842). Costs rose exponentially with the number of grade 3/4 ADRs and were highest in n = 20 cycles affected by more than four ADRs: €10 881 (€5455; 95% CI €4698–17064). They were 34 times higher than in cycles without severe toxicity and accounted for 21% of overall costs (Table 6). With €7093 (€4531; 95% CI €3299–8887), cycles affected by grade 3/4 infections were also identified as high-cost cycles compared with €500 (€57; 95% CI €413–588) for cycles without grade 3/4 infections. In cycles affected by at least one FN/FL episode, cost averaged €5170 (€2899; 95% CI €2993–7347), compared with €802 (€71; 95% CI €642–961) for cycles without FN/FL.

**sensitivity analysis**

Referring to sensitivity analyses, mean TMC-TC (€1032) was most sensitive regarding costs of hospital basic services. When varied according to its specific confidence limits (Figure 5), mean TMC-TC ranged from €890 to €1174 (±14%). Mean TMC-TC resulting from changes in various cost determinants were listed in descendent order.

Percental cost modifications of hospital basic services (Table 7) produced very similar results, with mean TMC-TC variation from €971 to €1124 (±6%; +9%).

**discussion**

Pressure on hospital health care budgets is constantly rising. In oncology, financing of innovative expensive therapies and therapy-induced complications with highly variable additional costs poses a special challenge. Therefore, we conducted this study to assess, under current practice patterns, the impact of CT-induced toxicity management on health resource consumption and cost.

**impact of toxicity in clinical practice**

Frequency data of CT toxicity typically come from randomised, controlled trials with selective recruitment and limited generalisability [28]. In contrast, our study gives an estimate of toxicity frequency in the clinical practice setting. In the observed NSCLC and LPD patient cohort, every second CT.

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**Table 3. Anticancer treatment**

<table>
<thead>
<tr>
<th></th>
<th>Treatment line (N = 286), % (n)a</th>
<th>LPD (n = 156), % (n)b</th>
<th>NSCLC (n = 130), % (n)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of CT visits</td>
<td>1531</td>
<td>735</td>
<td>796</td>
</tr>
<tr>
<td>No. of CT cycles</td>
<td>1004</td>
<td>619</td>
<td>385</td>
</tr>
<tr>
<td>Mean cycle number per treatment line</td>
<td>3.5</td>
<td>4.0</td>
<td>3.0</td>
</tr>
<tr>
<td>CT treatment lineb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>76.2 (218)</td>
<td>76.3 (119)</td>
<td>76.1 (99)</td>
</tr>
<tr>
<td>Second line</td>
<td>21.3 (61)</td>
<td>21.1 (33)</td>
<td>21.5 (28)</td>
</tr>
<tr>
<td>CT regime</td>
<td></td>
<td>46.8 (73) CHOP-like</td>
<td>77.7 (101) platinum-based</td>
</tr>
<tr>
<td>Not completing all preplanned CT cyclesd</td>
<td>33.2 (95)</td>
<td>12.8 (20)</td>
<td>57.7 (75)</td>
</tr>
<tr>
<td>Death</td>
<td>14.7 (14)</td>
<td>10 (2)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Tumour progression</td>
<td>47.4 (45)</td>
<td>30 (6)</td>
<td>52 (39)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>26.3 (25)</td>
<td>45 (9)</td>
<td>21.3 (16)</td>
</tr>
<tr>
<td>Treatment refusal</td>
<td>3.2 (3)</td>
<td>5 (1)</td>
<td>2.7 (2)</td>
</tr>
<tr>
<td>Other reasonsd</td>
<td>8.4 (8)</td>
<td>10 (2)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Predisposition to infection due to catheters or port systemsd</td>
<td>22.4 (64)</td>
<td>23.1 (36)</td>
<td>21.5 (28)</td>
</tr>
<tr>
<td>Radiation therapyf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6 weeks before CT</td>
<td>7.3 (21)</td>
<td>3.8 (6)</td>
<td>11.5 (15)</td>
</tr>
<tr>
<td>Concomitant to CT</td>
<td>10.8 (31)</td>
<td>1.3 (2)</td>
<td>22.3 (29)</td>
</tr>
</tbody>
</table>

aIf not otherwise stated.
bn = 7 missing.
cn = 20 missing.
dn = 6 not stated, n = 2 other reasons.
ecn = 26 missing.n = 6 missing.

CT, chemotherapy; LPD, lymphoproliferative disorder; NSCLC, non-small-cell lung cancer; CHOP, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone.
cycle was affected by at least one NCI–CTCAE grade 3/4 toxicity episode. Moreover, 40% of cycles were affected by at least one additional hospital visit or extension of hospitalisation due to toxicity. Therefore, the impact of CT-associated adverse events appears to be substantial both from a clinical and from an economic point of view. Including all prophylactic and therapeutic measures, TMC-TC amounted to €1032. This translates into an extra cost per patient of €3500 (data not shown).

### Cost of Toxicity Management

The bulk of economic literature on supportive care strategies comes from the United States [9, 10], where costs of a health care intervention usually range substantially higher than in Europe [11, 29, 30].

In contrast, variations between European cost estimates seem to be much lower. With €3841 mean cost per FN episode, the recently published Spanish study is broadly in line with the €4368 incremental TMC-CT attributable to our FN/FL subgroup (€5170 TMC-CT for patients with FN/FL minus €802 for patients without FN/FL). Therefore, the results seem to be transferable or easily adjustable to other health care systems and allow for identical or similar conclusions. To our knowledge, this is the first prospective longitudinal European analysis providing insight into the structure and distribution of TMC-CT.

Since toxicity management was covered mainly by the participating study centres, resource consumption between CT visits (e.g. consultation of a general practitioner) was estimated to be low. Thus, cost analysis was carried out from the hospital provider perspective. Indirect costs were not considered, as earlier German data had shown that the number of additional workdays lost as a result of CT-induced toxicity is low [2].

Accounting for ~70% of the total cost, hospitalisation is the cost driver; drugs and transfusions and other medical procedures produce another 30%. This highlights the fact that cost estimates solely based on the length of hospitalisation lead to an underestimation of true toxicity cost.

### Health Economic Impact, Clinical Implications and Further Research

With ~5% of cycles producing 56% of overall costs, the distribution of TMC-CT is highly asymmetric. As a consequence, mean TMC-TC (€1032) differs broadly from median costs (€86). Typically, mean costs serve as cost estimates in health economic models. Therefore, overestimation of cost-effectiveness could be the consequence.
Moreover, in the light of the observed high variability of TMC-TC in daily clinical care, hospital decision makers should interpret alleged differences in assumption-driven cost computations based on label-congruent regimens with caution. In this context, prospective studies or models incorporating observational data should be juxtaposed to

**Figure 2.** Treatment cycles with resource use (% of evaluable cycles, N = 1004). CINV, chemotherapy (CT)-induced nausea and vomiting; RBC, red blood cell; PLT, platelet; FFP, fresh frozen plasma; ATIII, antithrombin III. Excluding CT agents or health care consumption not directly related to CT-induced toxicity (e.g. cancer diagnostics, radiation therapy, surgery).

**Figure 3.** Toxicity management cost per treatment cycle: composition of total cost (total number of evaluable cycles, N = 1004). Cost of hospitalisation: hotel, staff, medical and non-medical consumables, overhead; all other expenditures were added. That is, dialysis, consults. Red blood cells, platelets, fresh frozen plasma, antithrombin III, albumin. NSCLC, non-small-cell lung cancer; LPD, lymphoproliferative disorder.

<table>
<thead>
<tr>
<th></th>
<th>NSCLC n=385</th>
<th>LPD n=619</th>
<th>All N=1004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital basic</td>
<td>905 [0]</td>
<td>677 [0]</td>
<td>764 [0]</td>
</tr>
<tr>
<td>services, staff</td>
<td>(677-1,133)</td>
<td>(495-859)</td>
<td>(622-907)</td>
</tr>
<tr>
<td>Medical procedures</td>
<td>10 [0]</td>
<td>19 [0]</td>
<td>15 [0]</td>
</tr>
<tr>
<td></td>
<td>(5-14)</td>
<td>(2-36)</td>
<td>(5-26)</td>
</tr>
<tr>
<td>Diagnostics</td>
<td>62 [0]</td>
<td>61 [0]</td>
<td>61 [0]</td>
</tr>
<tr>
<td></td>
<td>(39-85)</td>
<td>(40-82)</td>
<td>(46-77)</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>4 [0]</td>
<td>7 [0]</td>
<td>6 [0]</td>
</tr>
<tr>
<td></td>
<td>(1-7)</td>
<td>(1-14)</td>
<td>(2-10)</td>
</tr>
<tr>
<td>Blood products</td>
<td>60 [37]</td>
<td>55 [0]</td>
<td>57 [0]</td>
</tr>
<tr>
<td></td>
<td>(45-74)</td>
<td>(14-97)</td>
<td>(31-83)</td>
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<td></td>
<td>(67-126)</td>
<td>(102-193)</td>
<td>(98-198)</td>
</tr>
<tr>
<td>Total</td>
<td>1137 [169]</td>
<td>967 [29]</td>
<td>1032 [86]</td>
</tr>
<tr>
<td></td>
<td>(865-1409)</td>
<td>(695-1249)</td>
<td>(835-1239)</td>
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</table>
results from purely theoretical approaches like the recently published papers on the cost-effectiveness of pegfilgrastim versus filgrastim before reaching definite conclusions [31–33]. Similarly, asymmetric distribution of cost has been shown for FN [7], CT-induced thrombocytopenia and bleeding [16]. As a result, predictors for high TMC-TC should improve cost-effectiveness of current supportive care strategies. As our subgroup analyses reveal, TMC-TC depends on level of care, severity and number of ADRs. In cycles with grade 3/4 ADRs, TMC was 5.5-fold higher than in cycles without grade 3/4 toxicity. Mean TMC-TC cost rose exponentially with the number of grade 3/4 ADRs and was particularly high in cycles with more than four grade 3/4 ADRs (€10 881), ICU stay (€14 121), grade 3/4 infection (€7093) and FN/FL (€5071). Therefore, the reduction of severity grade and number of ADRs, as well as the avoidance of FN/FL and/or infections, are not only prominent clinical aims but also seem to have considerable economic implications. A risk-based approach to supportive care takes into account factors that predispose patients to an increased risk for severe toxic effects. Patient and treatment characteristics such as age, presence of leukaemia, hypovolaemia, comorbidities and infectious complications are associated with increased mortality, length of stay and cost due to FN [7, 34, 35]. Among patients with advanced-stage NSCLC, the pretreatment factors age, gender, performance status and white blood counts were reported to be significant predictors of severe adverse events [36].

Considerable research is focused on identifying the genetic basis of CT-induced toxicity [37, 38]. Ultimately, these genetic indicators may complement clinical parameters for individualising therapy. In recent years, the concept of toxicity clusters has emerged, suggesting that CT complications do not occur in isolation [39, 40]. Our data seem to support the sharing of a common pathogenesis for clustering toxic effects.

### Table 6. Toxicity management cost per treatment cycle (TC) stratified by subgroup (total number of evaluable cycles, N = 1004)

<table>
<thead>
<tr>
<th>Cycles</th>
<th>n</th>
<th>Mean (median) cost per TC in 2007 euros [95% CI]</th>
<th>Multiples of reference subgroup (mean)</th>
<th>% overall costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1004</td>
<td>1032 (86) [835–1230]</td>
<td>NA</td>
<td>100</td>
</tr>
<tr>
<td>No toxicity-associated hospital visitsa</td>
<td>633</td>
<td>62 (22) [51–73]</td>
<td>1.0 (ref.)</td>
<td>3.8</td>
</tr>
<tr>
<td>Toxicity-associated hospital visitsa</td>
<td>371</td>
<td>2688 (1016) [2199–3178]</td>
<td>43.4*</td>
<td>96.2</td>
</tr>
<tr>
<td>Only outpatient/day care</td>
<td>113</td>
<td>309 (228) [254–365]</td>
<td>5.0*</td>
<td>3.4</td>
</tr>
<tr>
<td>Normal outpatient/day care</td>
<td>239</td>
<td>2904 (1983) [2493–3315]</td>
<td>46.8*</td>
<td>67</td>
</tr>
<tr>
<td>Hospital visits with intensive care unit stay</td>
<td>19</td>
<td>14121 (8833) [8401–19 842]</td>
<td>227.6*</td>
<td>26</td>
</tr>
<tr>
<td>No toxicity grade 3/4</td>
<td>502</td>
<td>319 (30) [225–413]</td>
<td>1.0 (ref.)</td>
<td>15.5</td>
</tr>
<tr>
<td>Toxicity grade 3/4</td>
<td>502</td>
<td>1746 (197) [1372–2120]</td>
<td>5.5</td>
<td>84.5</td>
</tr>
<tr>
<td>1–2 ADRs grade 3/4</td>
<td>402</td>
<td>866 (113) [689–1042]</td>
<td>2.7*</td>
<td>33.6</td>
</tr>
<tr>
<td>3–4 ADRs grade 3/4</td>
<td>80</td>
<td>3884 (2601) [2727–5042]</td>
<td>12.2*</td>
<td>30.0</td>
</tr>
<tr>
<td>&gt;4 ADRs grade 3/4</td>
<td>20</td>
<td>10881 (5455) [4696–17064]</td>
<td>34.1*</td>
<td>21</td>
</tr>
<tr>
<td>No grade 3/4 infections</td>
<td>923</td>
<td>500 (57) [413–588]</td>
<td>1.0 (ref.)</td>
<td>44.5</td>
</tr>
<tr>
<td>Infections grade 3/4</td>
<td>81</td>
<td>7093 (4531) [5299–8887]</td>
<td>14.2*</td>
<td>55.4</td>
</tr>
<tr>
<td>No FN/FL</td>
<td>951</td>
<td>802 (71) [642–961]</td>
<td>1.0 (ref.)</td>
<td>73.6</td>
</tr>
<tr>
<td>FN/FL</td>
<td>53</td>
<td>5170 (2899) [2993–7347]</td>
<td>6.5*</td>
<td>26.4</td>
</tr>
</tbody>
</table>

*aOutpatient visits and inpatient admissions including extended hospitalisations.

*P < 0.05 versus reference group.

CI, confidence interval; NA, not applicable; ADR, adverse drug reaction; FN, febrile neutropenia; FL, febrile leukopenia.
Further research should describe toxicity clusters of high-cost cycles, as observed in this study, and define pretreatment factors predictive for high TMC.

In summary, our results reflect the high variability of CT-induced toxicity management cost in LPD and NSCLC patients. They confirm the value of real-world data to clarify treatment cost composition and distribution. Costs rose exponentially with the number of grade 3/4 ADRs and were particularly high in cycles affected by more than four ADRs, cycles with intensive care, and cycles affected by grade 3/4 infections and FN/FL. Asymmetric cost distribution highlights the need for individualised supportive care strategies. Future research should focus on identifying toxicity clusters and patient characteristics predictive for high costs.

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disclosure
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references


