The Pharmacoeconomic Benefits of Pemetrexed Dose Individualization in Patients With Lung Cancer

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Neutropenia is a dose-related treatment-limiting and costly adverse event of pemetrexed. We postulate that individualized dosing reduces the incidence of neutropenia. The aims of this study were (i) to investigate the costs of pemetrexed-related neutropenia and (ii) to determine the pharmacoeconomic benefits of individualized dosing of pemetrexed in terms of budget impact, yearly cost savings, and reduction in severe neutropenia. Retrospective data on the treatment of grade 3 or higher neutropenia during pemetrexed-based chemotherapy were collected from three Dutch hospitals to determine the mean healthcare consumption during a neutropenic episode. Subsequently, Monte Carlo simulations were performed using a validated pharmacokinetic/pharmacodynamic model to predict the neutropenia incidence during four cycles for standard dosing of pemetrexed and individualized dosing. The mean costs per neutropenia and the expected neutropenia incidence were combined to calculate the budget impact and cost savings. We found that the average costs per pemetrexed-associated neutropenic episode to be €1,490 (US $1,674). The neutropenia incidence for the standard and individualized pemetrexed dosing strategies were 12.7% and 9.9%, respectively. This resulted in total expected neutropenia-related costs of ~ €3.0 million (US $3.372 million) and €2.4 million (US $2.697 million), respectively. Taking the number of patients eligible for pemetrexed treatment into account, individualized dosing could result in saving €686,000 (US $770,995) on a yearly basis in the Netherlands alone. Individualized dosing of pemetrexed can decrease the incidence of neutropenia and thus result in a significant decrease in neutropenia-related costs and decreased risk of hospitalization or even death while maintaining therapeutic exposure.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Neutropenia can be dose-related treatment-limiting, and is known to be a costly adverse event of treatment with pemetrexed.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What are the real-world costs of pemetrexed-associated neutropenia and what is the budget impact of pemetrexed dose individualization?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Individualized dosing of pemetrexed can decrease the incidence of neutropenia and neutropenia-related costs and decrease the risk of hospitalization or even death without compromising efficacy.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Combined pharmacometric-pharmacoeconomic modeling may aid in decision making to implement pemetrexed dose individualization in the clinic.

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Pemetrexed is a classic cytotoxic drug from the class of antifolates that is widely used for the treatment of non-small cell lung cancer (NSCLC),[1] mesothelioma,[2] and thymoma.[3] Approximately 4,000 patients in the Netherlands are yearly treated with this drug,[4–7] either in combination with a platinum agent (with or without pembrolizumab) or as monotherapy.[1,4] Neutropenia is a dose-limiting toxicity of pemetrexed,[8] which occurs in 5–26% of the pemetrexed treated patients.[9–12] Neutropenia results in hospitalization in 9.5–18.1% of the patients with lung cancer and can eventually even lead to death in up to 10.5%.[13,14] Currently, pemetrexed is dosed based on body surface area (BSA).[8] Total systemic clearance of pemetrexed is primarily determined by renal function. Dosing based on BSA does not take renal function into account, and shows variability in exposure and pharmacodynamic response.[15,16] This variability results in unnecessary neutropenia as the toxicity of pemetrexed was shown to be related to its pharmacokinetics.[12,16] Dose individualization based on renal function will likely result in less toxicity; a simulation study by Latz *et al*. demonstrated that the risk of grade 3 neutropenia can be halved when pemetrexed is dosed based on renal function to reach a target area under the concentration-time curve (AUC) of 164 mg•h/L instead of BSA.[16]

The costs of treatment with pemetrexed are high: The reported total costs of treatment with pemetrexed and cisplatin in the Netherlands in 2013 were ~ €27,500 (US $30,907) per patient based on four 21-day treatment cycles with a pemetrexed dose of 500 mg/m^2 on Day 1.[4,8] These costs consist of both the high drug price and expensive treatments of adverse events such as neutropenia.[4,17] The reported treatment costs per patient for chemotherapy-induced nonfebrile neutropenia range from €1,400 (US $1,573) to €3,100 (US $3,484)[17–19] and the costs for febrile neutropenia can be up to €20,000 (US $22,478).[17,20] However, these numbers are outdated and the costs for neutropenia related to pemetrexed are unknown.

We postulate that by changing the dosing strategy for pemetrexed, the risk of developing neutropenia could be decreased, thereby significantly reducing the treatment costs. Therefore, the aims of this study were (i) to investigate the costs of pemetrexed-related neutropenia from a Dutch inpatient perspective and (ii) to determine the pharmacoeconomic benefits of individualized dosing of pemetrexed in terms of budget impact and yearly cost savings.

METHODS

The study consisted of three parts: first, determining the average costs of a pemetrexed-associated neutropenic episode based on real-world data; second, investigating the expected neutropenia incidence for different dosing strategies of pemetrexed. Finally, the outcomes were combined to calculate the budget impact and yearly cost savings.

Costs of pemetrexed-associated neutropenia

Multicenter data collection was done to calculate the average costs of a neutropenic episode from a Dutch inpatient perspective, based on average healthcare consumption during pemetrexed-based chemotherapy. All data were obtained during regular care and processed anonymously. The retrospective data set included data of three Dutch hospitals: Antoni van Leeuwenhoek Hospital (AvL) in Amsterdam, Jeroen Bosch Hospital (JBZ) in Den Bosch, and Radboud university medical center (Radboudumc) in Nijmegen. The collection of anonymized study data was approved by the local medical ethical review boards. Data of all patients who received at least one cycle of pemetrexed-based chemotherapy during the period (May 1, 2010–July 13, 2020 for AvL, February 1, 2014–February 1, 2019 for JBZ, and May 1, 2014–May 1, 2019 for RadboudUMC) were extracted from the electronic patient files. For the patients hospitalized in JBZ or RadboudUMC, data about the medication used were also available.

For each participant it was assessed whether a grade 3 or 4 neutropenia (absolute neutrophil count (ANC) or absolute leucocyte count < 1.0 × 10^9/L[21]) had developed during pemetrexed-based chemotherapy and whether clinical intervention was needed. For each neutropenic episode, the following treatment components were scored: emergency visits (yes/no), hospitalizations (yes/no, number of admission days and medication used), and number of extra white blood cell counts (WBCs).

To calculate the costs for an emergency visit and one admission day, the reference prices from "*Cost Guide – Methodology of Cost Research and Reference Prices for Economic Evaluations in Health Care*" were indexed to 2020 prices using the consumer price indexes of the Central Bureau of Statistics (CBS).[22,23] A weighted average was used to account for the difference in costs between hospitalizations in an academic and general hospital.[22] As medication costs were not included in the reference prices, these were calculated using the website of the Dutch National Healthcare Institute or obtained through the manufacturer.[24,25] In addition, the costs for WBCs were based on the tariffs of the top four Dutch healthcare insurers (covering 85% of the insured population).[26,27] Finally, the calculated costs multiplied by the mean care consumption during a neutropenic episode yielded the expected costs.

Evaluation of pemetrexed-associated neutropenia

Two scenarios were investigated to subsequently assess the expected incidence of neutropenia: standard dosing according to drug label (500 mg/m^2) and individualized dosing based on renal function. The individualized dosing algorithm was derived from a pharmacokinetic model,[15] using absolute estimated glomerular filtration rate (eGFR) calculated with the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation[28] and a target AUC of 164 mg•h/L (this AUC corresponds with the exposure of a "typical individual" receiving 500 mg/m^2; see ref. 16). This resulted in the following dosing equation: dose = 109 × (weight/70)$^{0.75}$ + 561 × (eGFR/75). To account for overestimation of renal function, dose was capped at an eGFR of 120 mL/min (as is done in clinical practice).

Monte Carlo simulations were performed using the nonlinear mixed effect modeling software package NONMEM V7.4 (Icon, Dublin, Ireland). We used a validated pharmacokinetic/pharmacodynamic model for pemetrexed pharmacokinetics and their relationship with induced neutropenic response (for vitamin B12 and folic acid-supplemented patients). In short, the pharmacokinetic model consisted of a three-compartment disposition model for pemetrexed with eGFR as a covariate for clearance. The pharmacokinetic model was coupled with a mechanistic myelosuppression model describing the time course of ANC during cytotoxic treatment, where the proliferation rate in the progenitor cell compartment was inhibited by the pemetrexed concentration. The model is described in detail by Boosman *et al*.[29] A population of 500 participants was simulated for each scenario. Weights and heights were derived from the National Health and Nutrition Examination Survey (NHANES) database (median body mass index = 26.2 kg/m^2, comparable to baseline body mass index of patients with lung cancer[30]).[31] Baseline eGFR (calculated with CKD-EPI) was simulated from a normal distribution based on the population as described by Latz *et al*. (2006) (median 90 mL/min/1.73 m^2, coefficient of variation (CV) 32%[16]) and decline of renal function over time as a result of treatment with pemetrexed was coded as a linear function based on a recent study in patients with lung cancer treated with pemetrexed (slope −0.0021 mL/min/1.73 m^2 per hour, CV 120%).[21] For each participant, eGFR (per

1.73 m^2) was recalculated to absolute eGFR using BSA. Baseline ANC was also simulated from a normal distribution based on the population described by Boosman *et al.*[29] (median 5.3 × 10^9/L, CV 37%).

As the median number of pemetrexed cycles is four in clinical practice,[32] intended treatment consisted of four 21-day cycles with pemetrexed administration on Day 1 for each participant. For each cycle, the expected nadir ANC was read out on Day 9 as the reported nadir ANC is between Day 8 and 10 for pemetrexed.[8] In addition, ANC and eGFR on Day 19 were evaluated, as those determined eligibility for the subsequent cycle. Decision options were according to the drug label and included: continue as planned, dose reduction to 75% (when ANC at Day 9: < 0.5 × 10^9/L), postpone next cycle with one week (when ANC at Day 19: < 1.5 × 10^9/L) or cease treatment (when eGFR drops below/under 45 mL/min OR when a third dose reduction is required).[8]

For each scenario, the following parameters were collected: neutropenia counts, dose reductions and treatment delays, and per participant the nadir ANC on Day 9, ANC and eGFR on Day 19 (and Day 26 if applicable), and pemetrexed AUC. These parameters were used to calculate the incidences of neutropenia, dose reductions, and treatment delays. We expected that the effect of dose individualization would be greater in patients with a decreased eGFR. Therefore, the effect was also assessed in two subgroups for each scenario: eGFR < 90 mL/min and ≥ 90 mL/min at baseline since the median eGFR was 90 mL/min.

Pharmacoeconomic evaluation

The number of CTCAE grade 3 or 4 neutropenic episodes[21] a patient would experience on average during a treatment of four 21-day cycles was determined. This number was multiplied by the average costs of a neutropenic episode and by the number of estimated patients who are yearly treated with pemetrexed in the Netherlands (n = 4,000[4–7]) to assess budget impact. In addition, the expected cost savings of individualized dosing relative to standard dosing were calculated.

Sensitivity analysis

One-way sensitivity analyses (tornado diagram) were performed to test the robustness of the calculated cost savings. The following parameters (lower limit; upper limit) were included in the sensitivity analyses: medication costs during admission (lower and upper limit determined in this study), costs of one extra WBC (lower and upper limit determined in this study), interindividual variability (IIV) of baseline eGFR (CV 16% as this is found in the study of de Rouw *et al.*[32]; upper limit was not tested as a higher IIV is not found in previous studies), and IIV of baseline ANC (CV 30%; CV 45%[29]).

Descriptive statistics

Descriptive statistics were used to calculate the following parameters for the retrospective data set: median (with interquartile range (IQR)) nadir ANC, incidence of grade 3/4 neutropenia, mean (± standard deviation (SD)) healthcare consumption per treatment component, and mean (± SD) medication costs during hospitalization. The following parameters were calculated with descriptive statistics: mean administered pemetrexed dose, incidences of grade 3/4 neutropenia, dose reductions, treatment delays and discontinuations, and medians (with IQR) of the AUC of pemetrexed.

RESULTS

Costs of pemetrexed-related neutropenia

We retrospectively identified 1,485 patients who received at least one cycle of pemetrexed-based chemotherapy during the study period. Overall, 197 patients experienced 256 pemetrexed-associated neutropenic episodes with a median nadir ANC of 0.70 × 10^9/L (IQR = 0.50–0.81), giving a grade 3/4 neutropenia incidence of 13.3%. The hospitalization of two patients differed greatly from the others in terms of the number of admission days. These neutropenic episodes were diagnosed at the end of a long hospitalization due to another reason. Therefore, these two patients were excluded from further analyses.

Table 1 summarizes the mean healthcare consumption during a neutropenic episode and the costs involved. Half of the neutropenic episodes did not require any treatment (129 of 256). The similar percentages of emergency visits (26.4%) and hospitalization (28.0%) indicate that hospitalization was required in most cases of an emergency visit. Duration of hospitalization was on average 2.48 days (SD = 5.31) and always on a general ward (100%). In addition, on average 1.39 (SD = 2.43) extra WBCs were performed per neutropenic episode. The costs per neutropenic episode were calculated by multiplying the mean healthcare consumption by the costs per unit.

This resulted in total average treatment costs of €1,490 (US $1,674) per neutropenic episode. Admission to a general ward was the main cost driver, representing 85.7% of the total costs. Medication costs per patient ranged from €0 to €2,100 (US $2,360) with mean costs of €448 (US $503) (SD = €553 (US $621)). Costs of one extra WBC were €10.37 (US $11.60).

Table 1 Overview of mean care consumption (n = 254) and costs per treatment component

Treatment component	Mean care consumption	Costs per unit	Costs per neutropenic episode
Emergency visit	26.4%	€280 (US $315)	€74 (US $83)
Hospitalization	28.0%	€448[a] (US $503)	€125 (US $140)
Admission days at ICU, mean (±SD)	0 (0)	€1,283 (US $1,442)	€0
Admission days at general ward, mean (±SD)	2.48 (5.31)[b]	€515[c] (US $579)	€1,277 (US $1,435)
Extra WBC, mean (±SD)	1.39 (2.43)	€10.37 (US $11.60)	€14 (US $16)
Total		—	€1,490 (US $1,674)

The costs per neutropenic episode were calculated by multiplying the mean care consumption by the costs per unit. A unit was seen as one emergency visit, one hospitalization, one admission day, or one extra WBC.
ICU, intensive care unit; SD, standard deviation; WBC, white blood cell count.
[a]This amount represents the average medication costs during one hospitalization as those were not included in the price of admission to the ICU or general ward.
[b]One patient was admitted to the emergency department during hospitalization, which is more comparable to admission to a general ward than to the ICU. Therefore, it was included as hospitalization on a general ward.
[c]No data were available about the average costs of one admission day at the (lung) oncology ward. Therefore, the weighted average (based on the ratio of admission days in general and academic hospitals) of the reference price of a general ward was taken.

Table 2 Outcomes simulation of neutropenic response per dosing regimen

Dosing strategy	Standard	Individualized
Cycles, *n* (%)	1,907 (100)	1,926 (100)
Dose pemetrexed, mg, mean (±SD)	904 (118)	803 (181)
AUC, mg·h/L, median (IQR)	181 (144–224)	158 (136–183)
Incidence neutropenia, %	12.7	9.9
<90 mL/min	17.2	11.0
≥90 mL/min	9.8	9.0
Incidence dose reductions, %	3.4	1.1
<90 mL/min	5.5	1.5
≥90 mL/min	1.9	0.8
Incidence delays, %	1.1	0.9
<90 mL/min	2.0	1.3
≥90 mL/min	0.5	0.7
Discontinued, *n* (%)	31 (6.4)	27 (5.5)
Due to nephrotoxicity	15 (3.1)	25 (5.1)
Due to hematotoxicity	16 (3.3)	2 (0.4)

AUC, area under the concentration-time curve; IQR, interquartile range; SD, standard deviation.

Evaluation of pemetrexed-associated neutropenia

The outcomes of this evaluation are presented in **Table 2**. After four treatment cycles, the incidence of all three types of events (neutropenia, dose reduction, and treatment delay) was higher in the standard dosing group (12.7%, 3.4%, and 1.1%, respectively) compared with the individualized dosing group (9.9%, 1.1%, and 0.9%, respectively). Furthermore, discontinuation due to hematological toxicity was more common in the standard dosing group (3.3% vs. 0.4% for individualized dosing), in line with the higher neutropenia incidence in this group. **Figure 1** visualizes the differences in neutropenia incidence between the two groups, when divided in two subgroups (baseline eGFR < 90 and ≥ 90 mL/min). Differences in neutropenia incidence were more pronounced in the subgroup with a baseline eGFR <90 mL/min.

Pharmacoeconomic evaluation

Table 3 presents the values used for the calculation of the budget impact. Based on the expected neutropenia incidence, we predict that, on average, a patient experiences 0.509 neutropenic episodes during a treatment of four 21-day pemetrexed cycles with the standard dosing regimen. Using the calculated treatment costs of €1,490 (US $1,674) per neutropenic episode and the total number of expected pemetrexed-treated patients in the Netherlands of 4,000,[4–7] we calculated yearly neutropenia treatment costs of ~ €3.0 million (US $3.372 million) with the standard dosing strategy.

Changing the dosing strategy from standard to individualized resulted in a decrease in the number of neutropenic episodes during median treatment from 0.509 to 0.395. This correlates with yearly treatment costs of ~ €2.4 million (US $2.697 million), resulting in expected yearly cost savings of €686,001 (US $770,998). The difference in decrease in neutropenia incidence between the eGFR subgroups indicates that ~ 80% of cost savings is due to changing the dose strategy in patients with eGFR < 90 mL/min.

The results of the one-way sensitivity analyses are shown in the tornado diagram in **Figure 2**. The tornado diagram indicates that the cost savings were most sensitive to the change in the interindividual variability on baseline eGFR. Decreasing the IIV to the lower bound of 16% led to cost savings of €355,874 (US $399,967). No upper boundary was set as described in the methods section. Decreasing and increasing the IIV on ANC to the boundaries of 30% and 45% resulted both in increased yearly cost savings for individualized dosing of €742,689 (US $834,708) and €687,397 (US $772,565), respectively. The lower and upper limits

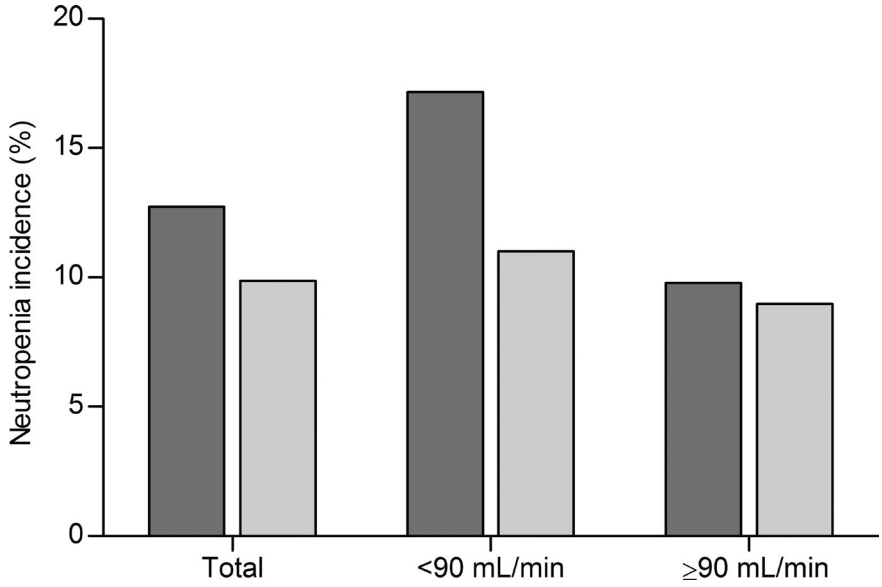

Figure 1 Neutropenia incidence in standard dosing group vs. individualized dosing group, assessed per subgroup based on renal function. Dark gray: standard dosing; light gray: individualized.

Table 3 Values used to calculate the budget impact

	Standard	Individualized
Neutropenia incidence	12.7%	9.9%
Number of neutropenic episodes during median treatment of four cycles	0.509	0.395
Costs neutropenia during median treatment of four cycles	€759 (US $853)	€588 (US $661)
Number of patients	4,000	4,000
Budget impact neutropenia	€3,037,819 (US $3,414,205)	€2,351,817 (US $2,643,207)
Cost savings	N/A	€686,001 (US $770,998)

Multiplying the number of neutropenic episodes with €1,490 (US $1,674) (= costs per neutropenic episode) gave the costs for neutropenia during median pemetrexed treatment. This amount is multiplied by the number of patients to obtain the budget impact.
N/A, not applicable.

for mean medication costs were determined to be €367 (US $412) and €476 (US $535), based on if either solely the cheapest products or solely the most expensive products were described (according the Dutch National Healthcare Institute[24]). The limits for the costs of the WBCs were based on the lowest and highest tariffs of the top four health insurers as mentioned in the methods section. This resulted in a lower limit of €7.40 (US $8.32) and upper limit of €15.35 (US $17.25). Changes in both the medication costs and the costs of one extra WBC minimally influenced the cost savings.

DISCUSSION

As it stands, this is the first study to investigate the costs of specifically pemetrexed-associated neutropenia and to explore the budget impact of standard and individualized pemetrexed dosing. We found that the average treatment costs per pemetrexed-associated neutropenic episode were €1,490 (US $1,674) from a Dutch inpatient perspective. The neutropenia incidence for the standard and individualized pemetrexed dosing strategies were 12.7% and 9.9%, respectively, resulting in total expected neutropenia treatment costs of ~ €3.0 million (US $3.372 million) and €2.4 million (US $2.697 million), respectively. This implies that total yearly cost savings could be €686,001 (US $770,998) for individualized dosing relative to standard dosing. As pemetrexed is an expensive drug, cost savings could even be higher if taking into account the lower mean dose administered in the individualized dosing group. Moreover, by reducing neutropenia incidence, the risk of hospitalization or even neutropenia-related death can be decreased.[13,14]

Several studies looked at generally chemotherapy-induced neutropenia instead of specifically pemetrexed-associated neutropenia.[17–19] Most studies differentiate between costs due to nonfebrile and febrile neutropenia. The reported costs vary from €1,400 (US $1,573) to €3,100 (US $3,484) for nonfebrile[17–19] and from €3,900 (US $4,383) to €20,000 (US $22,478) for febrile neutropenia.[17,20,33] When comparing our results to previous research, we found that our costs fell in the range of reported costs for nonfebrile neutropenia.[17–19] This was not surprising considering the low incidence

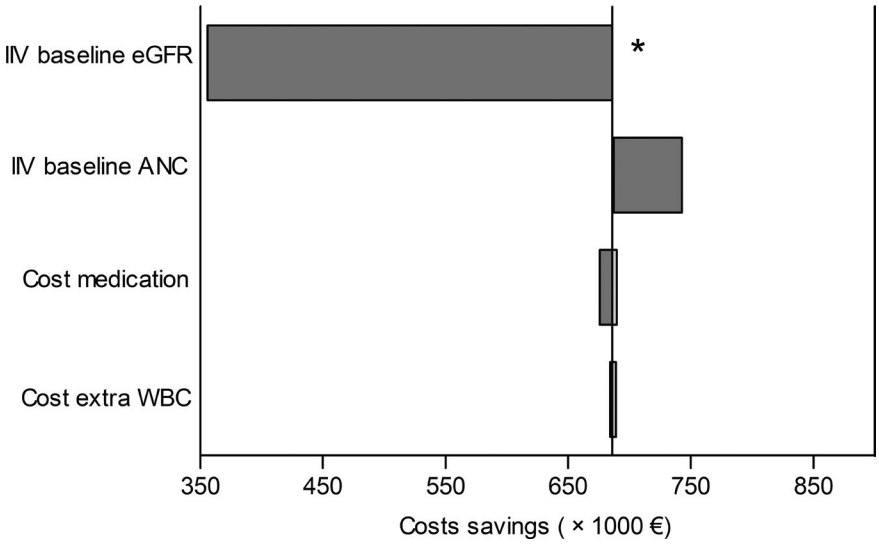

Figure 2 Tornado diagram showing results of the one-way sensitivity analyses. Dark gray: lower limit; light gray: upper limit. *Upper limit not tested as a higher IIV is not rational. Note: effect of upper limit IIV baseline ANC was €687,397 (US $772,565) and thus only €1,000 (US $1,124) from y-axis. Used LLs (lower limits) and ULs (upper limits) were as follows for all parameters: IIV baseline eGFR LL = 16%,[32] UL = not tested (see*); IIV baseline ANC LL = 30%, UL = 45%;[29] cost medication LL = €376 (US $423), UL = €476 (US $535); cost extra WBC LL = €7.40 (US $8.32), UL = €15.35 (US $17.25). ANC, absolute neutrophil count; eGFR, estimated glomerular filtration rate; IIV, interindividual variability; WBC, white blood cell count.

of febrile neutropenia with pemetrexed treatment in other clinical studies (0–1.9%).[10,34,35] Febrile neutropenia may involve admission on an intensive care unit[36,37] (€1,283 (US $1,442) per admission day[22]) and treatment with granulocyte colony-stimulating factor (G-CSF)[17–19] (~ €900 (US $1,012) per treatment[24]), which can increase the treatment costs dramatically. These treatment components were not required in our patient cohort, which resulted in costs comparable to that for nonfebrile neutropenia.

We identified a grade 3/4 neutropenia incidence of 13.3% based on real-world data. Phase III trials showed a grade 3/4 neutropenia incidence of 5–26%.[9–12] In the clinical setting, determination of nadir ANC may not always be part of standard care if symptoms are absent, as expected nadir of the ANC lies around Day 8–10 and routine blood chemistry is often performed a few days prior to the new treatment cycle (Day 18–21). Thus, in routine clinical care a lower incidence may be observed than we predict. Nonetheless, we found an incidence of 12.7%, which is comparable to the findings in our clinical retrospective data set. This implies that we can translate the findings of our analyses to the clinical setting.

Differences in neutropenia incidence between standard dosing and individualized dosing were more pronounced in the subgroup with baseline eGFR < 90 mL/min. Because standard dosing does not take renal clearance into account, patients with a lower eGFR have a higher exposure to pemetrexed. As this inversely correlates with toxicity,[12,16] these patients have a higher risk of developing neutropenia compared with patients with a normal eGFR. Since renal function is incorporated in the individualized dosing equation, this dosing strategy resulted in less frequent neutropenia in the lower eGFR group, as expected. This indicates that patients with eGFR < 90 mL/min would benefit the most from changing the dosing strategy. Since more than 80% of the NSCLC patients are aged > 60 years[5] and the elderly have a decreased eGFR[38] (75% have an eGFR of < 90 mL/min[39,40]), an individualized dosing strategy is favorable for a large part of the pemetrexed-treated population.

No effect on pemetrexed efficacy is expected by changing its dosing strategy as we used a target AUC of 164 mg·h/L for individualized dosing, which corresponds with the exposure of a typical individual dosed according to the drug label (500 mg/m^2, with BSA 1.81 m^2 and creatinine clearance of 96.6 mL/min[16]). Thus, effective exposure will be achieved with individualized dosing of pemetrexed. It may even be argued that changing to an individualized dosing strategy leads towards better therapy in patients with low BSA with high eGFR as their exposure is relatively low with the standard dosing strategy.[16] Moreover, we found that fewer participants needed a dose reduction in the individualized dosing group compared with the standard dosing group. Hence, the number of suboptimally treated patients could possibly be decreased with an individualized dosing strategy compared with standard dosing.

A strength of our study was that data were incorporated from three different Dutch types of hospitals (a cancer-specialized, general, and academic hospital), making the outcome representative for the Dutch clinical setting. Some limitations of the study may remain. First, data on resource use during pemetrexed-associated neutropenia were collected retrospectively, and therefore not all data may have been recorded in the electronic patient file. Second, a hospitalization or emergency visit could be primarily due to another reason with neutropenia as an incidental finding. This might give an overestimation of the costs. Nonetheless, in those cases neutropenia was one of the reasons for hospitalization thus reflecting clinical practice. However, the reason of hospitalization was checked for patients with a high number of admission days compared with the others, and these were excluded from further analyses if applicable.

One-way sensitivity analyses showed that the calculated yearly cost savings were robust for the changes in all parameters except for IIV on eGFR. As expected, changing the interindividual variability on baseline eGFR had a major impact since the differences in neutropenia incidence were most pronounced in the lower eGFR group and narrowing the variability would result in fewer participants with a decreased renal function. However, taking into account the higher prevalence of lung cancer in the elderly and their diminished renal function,[5,38] the pemetrexed-treatable population is expected to include a relatively large number of patients with a lower renal function, which is better reflected by a high variability on renal function. Also, changing the variability in renal function still resulted in expected yearly savings of ~ €356,000 (US $400,108).

In conclusion, the results provide strong evidence that changing the dosage strategy of pemetrexed from standard to individualized is favorable for both patient and payer as it results in a decreased neutropenia incidence, especially in patients with an eGFR < 90 mL/min. This will probably result in less hospitalization and mortality in the treated population. In addition, the pemetrexed treatment costs will be decreased by implementing individualized dosing of pemetrexed, resulting in expected yearly cost savings of €686,000 (US $770,998). A clinical study is currently conducted to assess the feasibility of individualized dosing using renal function and to find a safe dose in patients with renal impairment (clinicaltrials.gov identifiers NCT03655821 and NCT03656549). Other options to reduce toxicity, such as a lower dose or standard folinic acid rescue could also be explored in prospective trials.

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CONFLICTS OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

N.d.R., M.d.B., R.J.B., M.M.v.d.H., D.M.B., J.E.L., H.J.D., G.W.J.F., and R.t.H. wrote the manuscript. N.d.R., M.d.B., R.J.B., M.M.v.d.H., D.M.B., J.E.L., H.J.D., G.W.J.F., and R.t.H. designed the research. N.d.R., M.d.B., R.J.B., J.E.L., and R.t.H. performed the research. N.d.R., M.d.B., R.J.B., G.W.J.F., and R.t.H. analyzed the data.

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