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# Timing of Severe Toxicity from Chemotherapy in Patients With Lung Cancer

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**Abstract.** *Background/Aim: The aim of this study was to investigate the timing of severe toxicity in lung cancer patients receiving chemotherapy. Patients and Methods: Patients with advanced non-small cell lung cancer or limited disease small cell lung cancer included in two randomized controlled trials were analysed. Severe toxicity was defined as grade 3-5 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Results: We analysed 569 patients and 433 (76.1%) experienced severe toxicity. Of these, 249 (57.5%) experienced the first episode of severe toxicity after the first, 109 (25.2%) after the second, 54 (12.5%) after the third and 18 (4.2%) after the fourth course of chemotherapy. Performance status (PS 2 vs. 0-1; p=0.046) and treatment arm were independent predictive factors for severe toxicity. Conclusion: Severe toxicity was most frequent after the first chemotherapy course, but some patients did not experience severe toxicity until after the fourth course. Accounting for timing might be important when studying factors predicting severe toxicity.*

Severe toxicity is frequent among cancer patients who receive chemotherapy. Such toxicity causes discomfort and poor quality of life, might be life-threatening, while treatment of side-effects requires a lot of attention and resources from the health care services (1, 2).

There are several possible causes for severe toxicity. In some cases, it is caused by a very high initial dose, while toxicity occurring later may be due to exhaustion of an organ system, *e.g.* the bone marrow reserves (3). The different underlying reasons are not necessarily interrelated and may confound studies of risk factors, since few studies have accounted for which time point during chemotherapy severe toxicity occurs. We are only aware of one study of 4458 patients with solid tumours or lymphoma receiving four courses of chemotherapy (4). The occurrence of neutropenic fever was highest after the first course, but the study did not include information about the effect of dose-reductions or delays of subsequent courses. In addition, it provided limited data on types of toxicity and long-term outcomes and no data on predictive factors for early or late toxicity.

In this study, we aimed to investigate the timing of severe toxicity during the chemotherapy treatment period for lung cancer patients enrolled in two randomized controlled trials. We also examined whether there were differences in the type of severe toxicity at different timepoints, the associations between toxicity and baseline characteristics and associations with overall survival. Lung cancer patients have a relatively high age, a majority has significant comorbidity, and severe toxicity is common. Thus, we believe that these cohorts were suitable for this exploratory study.

## Patients and Methods

*Design and approvals.* This study is an analysis of patients from two Norwegian randomized controlled trials (RCTs) on lung cancer patients. All patients gave written consent. Both RCTs and the present study were approved by the Regional Committee for Medical Research Ethics in Central Norway.

*Patients and study treatment.* The PEG trial was an open, randomized, multicentre phase III study comparing gemcitabine/carboplatin (GC) and pemetrexed/carboplatin (PC) as first-line chemotherapy in stage IIIB or IV non-small-cell lung cancer (NSCLC) (5). The study enrolled 436 patients with performance status 0-2 from April 2005 to July 2006. Patients were randomized to receive four courses of pemetrexed (500 mg/m$^2$) plus carboplatin

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*Key Words:* Lung cancer, chemotherapy, toxicity, predictive, prognostic.

Table I. *Patient characteristics, timing of toxicity and treatment completion.*

| | Total population n=569 | | First toxicity after 1st course n=249 | | First toxicity after 2nd-4th course n=181 | | No severe toxicity n=133 | | Received four courses n=428 | | Received ≤ three courses n=141 | | Dose reductions and/or delays of courses n=273 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline characteristics | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| Gender | | | | | | | | | | | | | | |
| Male | 315 | 55.4 | 146 | 58.6 | 91 | 50.3 | 73 | 54.9 | 237 | 55.4 | 78 | 55.3 | 145 | 53.1 |
| Female | 254 | 44.6 | 103 | 41.4 | 90 | 49.7 | 60 | 45.1 | 191 | 45.6 | 63 | 44.7 | 128 | 46.9 |
| Age | | | | | | | | | | | | | | |
| ≥75 | 87 | 15.3 | 43 | 17.3 | 18 | 9.9 | 26 | 19.5 | 64 | 14.9 | 23 | 16.3 | 35 | 12.8 |
| <75 | 482 | 84.7 | 206 | 82.7 | 163 | 90.1 | 107 | 80.5 | 364 | 85.1 | 118 | 83.7 | 238 | 87.2 |
| Median (range) | 64 (25-90) | | 66 (37-84) | | 62 (25-85) | | 63 (37-90) | | 64 (25-85) | | 64 (35-90) | | 64 (40-85) | |
| Stage | | | | | | | | | | | | | | |
| 1 | 13 | 2.3 | 6 | 2.4 | 5 | 2.8 | 2 | 1.5 | 12 | 2.8 | 1 | 0.7 | 10 | 3.7 |
| 2 | 16 | 2.8 | 5 | 2.0 | 10 | 5.5 | 1 | 0.7 | 14 | 3.3 | 2 | 1.4 | 11 | 4.0 |
| 3 | 232 | 40.8 | 109 | 43.8 | 80 | 44.2 | 41 | 30.8 | 188 | 43.9 | 44 | 31.2 | 132 | 48.4 |
| 4 | 293 | 51.5 | 125 | 50.2 | 77 | 42.5 | 88 | 66.3 | 200 | 46.7 | 93 | 66.0 | 109 | 39.9 |
| Unknown | 15 | 2.6 | 4 | 1.6 | 9 | 5.0 | 1 | 0.7 | 14 | 3.3 | 1 | 0.7 | 11 | 4.0 |
| Performance status | | | | | | | | | | | | | | |
| 0 | 141 | 24.8 | 59 | 23.7 | 44 | 24.3 | 36 | 27.1 | 115 | 26.9 | 26 | 18.4 | 68 | 24.9 |
| 1 | 319 | 56.1 | 131 | 52.6 | 107 | 59.1 | 78 | 58.6 | 246 | 57.5 | 73 | 51.8 | 156 | 57.1 |
| 2 | 109 | 19.1 | 59 | 23.7 | 30 | 16.6 | 19 | 14.3 | 67 | 15.6 | 42 | 29.8 | 49 | 18.0 |
| Histology | | | | | | | | | | | | | | |
| Squamous | 100 | 17.5 | 44 | 17.7 | 27 | 14.9 | 29 | 21.8 | 73 | 17.1 | 27 | 19.1 | 38 | 13.9 |
| Adeno | 203 | 35.7 | 80 | 32.1 | 60 | 33.2 | 61 | 45.9 | 140 | 32.7 | 63 | 44.7 | 79 | 28.9 |
| Other NSCLC | 109 | 19.2 | 51 | 20.5 | 23 | 12.7 | 32 | 24.0 | 79 | 18.4 | 30 | 21.3 | 39 | 14.3 |
| SCLC | 157 | 27.6 | 74 | 29.7 | 71 | 39.2 | 11 | 8.3 | 136 | 31.8 | 21 | 14.9 | 117 | 42.9 |
| Treatment | | | | | | | | | | | | | | |
| Pemetrexed Carboplatin | 208 | 36.6 | 55 | 22.1 | 58 | 32.0 | 92 | 69.2 | 157 | 36.7 | 51 | 36.2 | 60 | 22.0 |
| Gemcitabin Carboplatin | 204 | 35.8 | 120 | 48.2 | 52 | 28.8 | 30 | 22.5 | 135 | 31.5 | 69 | 48.9 | 96 | 35.2 |
| Cisplatin Etoposide | 157 | 27.6 | 74 | 29.7 | 71 | 39.2 | 11 | 8.3 | 136 | 31.8 | 21 | 14.9 | 117 | 42.8 |

(Area Under the Curve, AUC=5) on day 1 or gemcitabine (1000 mg/m2) on day 1 and 8 and carboplatin (AUC=5) on day 1 every three weeks. There were no significant differences in health-related quality of life or overall survival, but patients on the gemcitabine-arm experienced more hematologic toxicity.

The HAST trial was an open, randomized, multicentre phase II trial comparing twice-daily thoracic radiotherapy (TRT) of 45 Gy with once-daily TRT of 42 Gy in limited disease small cell lung cancer (LD SCLC) (6). Between May 2005 and January 2011, 157 patients were enrolled. Patients were to receive four courses of cisplatin (75 mg/m$^2$) on day 1 and etoposide (100 mg/m$^2$) on day 1-3, every three weeks. There were no statistically significant differences in overall survival, but patients receiving twice-daily TRT had 6 months longer median overall survival. There were no significant differences in chemo- or radiotoxicity.

In the PEG trial, patients ≥75 years of age had a 25% dose reduction from the first chemotherapy course. In both studies, chemotherapy doses were to be reduced by 25% if haematological values on day 22 were as following: leucocytes 2.5-2.9×10$^9$/l or platelets 75-99×10$^9$/l (HAST); or absolute neutrophil count (ANC) 1.0-1.49×10$^9$/l or thrombocytes were 75-99×10$^9$/l (PEG). If the values were lower, the course was to be delayed until resolution followed by a 25% dose reduction. Furthermore, in the PEG trial, a 25% dose reduction was to be performed if nadir ANC was <0.5×10$^9$/l and platelets were ≥50×10$^9$/l, and a 50% reduction if platelets were ≤50×10$^9$/l.

In both studies dose reductions were maintained for all subsequent courses. Treatment was discontinued if a patient qualified for a third dose reduction, or if a course was postponed more than three weeks due to toxicity.

*Inclusion criteria*. Patients who received at least one chemotherapy course were eligible for the present study provided complete toxicity data were available.

*Assessments*. The Common Terminology Criteria for Adverse Effects (CTCAE) v3.0 was used for classification of toxicity in both studies (7). We defined severe toxicity as CTCAE grade 3-5, and excluded radiotoxicity (*e.g.* pneumonitis or esophagitis) in our analyses.

*Statistical considerations*. Toxicity data were compared using Pearson's Chi-square test and logistic regression adjusting for baseline characteristics. Survival was defined as time from randomization until death and was estimated using the Kaplan-Meier method and

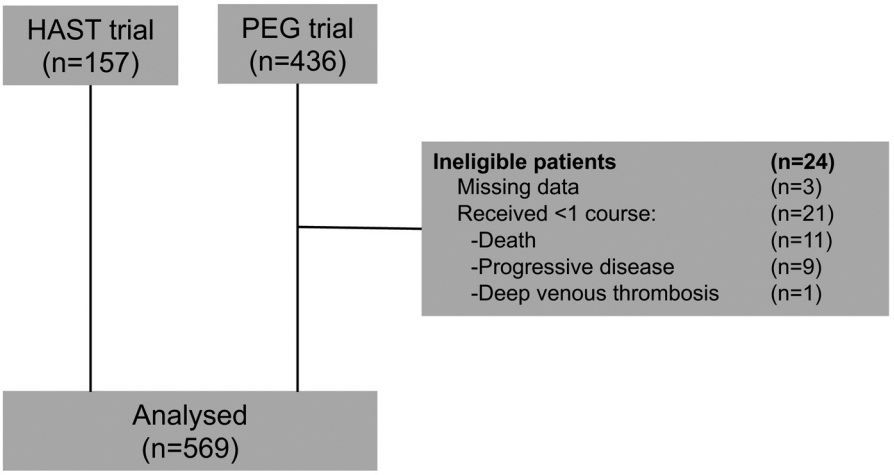


Figure 1. *Twenty-four patients from the PEG trial were excluded from analyses.*

compared using the log-rank test. Multivariable survival analyses were performed using the Cox proportional hazard method adjusting for baseline characteristics. The level of significance was defined as a two-sided $p<0.05$ and statistical analyses were performed using SPSS version 25 (IBM, New York, USA).

## Results

*Patients.* All 157 patients enrolled in the HAST trial, and 412 of 436 patients (94.4%) from the PEG trial were included in the present study. Toxicity data were incomplete in three cases, and 21 patients did not complete the first course due to death (n=11), progressive disease (n=9), and deep venous thrombosis (n=1) (Figure 1).

Median age in our study cohort was 64 years, 15.3% were ≥75 years; 55.4% were men; 40.8% had stage III and 51.5% stage IV; 80.9% had PS 0-1; and 72.4% NSCLC (Table I). Median follow up for survival was 90 months for HAST patients and 19 months for PEG patients.

*Chemotherapy administered.* Forty-eight (8.4%) patients received one course, 45 (7.9%) two courses, 48 (8.4%) three courses, and 428 (75.2%) four courses; 36.6% received pemetrexed/carboplatin (PC), 35.9% gemcitabine/carboplatin (GC), and 27.6% cisplatin/etoposide (PE). The mean number of courses was 3.5 for PC, 3.3 for GC and 3.8 for PE.

The total number of patients with any dose reduction after the first course was 213 (37.4%), and 142 (25.0%) patients had treatment delays. Grade 3-4 toxicity was the most common cause for treatment delays and/or reductions (78.2%), while 14.9% were caused by grade 1-2 toxicity and 6.9% by other reasons, such as holidays.

*Toxicity.* In total, 433 (76.1%) experienced severe toxicity during treatment, 397 (69.8%) experienced hematologic and 176 (30.9%) non-haematological toxicity. Of the 433 patients with severe toxicity, 249 (43.8%) patients experienced grade 3-5 toxicity after the first, 237 (45.5%) after the second, 245 (51.5%) after the third, and 174 (40.7%) after the fourth course (Figure 2).

The most frequent severe haematological toxicities were neutropenia (52.7%), leukopenia (48.5%) and thrombocytopenia (37.8%) (Figure 3). Neutropenic infection (10.9%), infection without neutropenia (7.9%) and neutropenic fever (5.6%) were the most common non-haematological toxicities (Figure 3).

There were 62 deaths during the study treatment period, most commonly due to progressive disease (n=34), neutropenic infections (n=8), and infections without neutropenia (n=6). Thirty-one deaths occurred after the first course, eighteen after the second, six after the third, and seven after the fourth course.

*Associations between baseline characteristics and severe toxicity.* PE patients had the highest and PC patients the lowest risk of experiencing severe toxicity, both in the uni- (PE: 93.0%, GC: 85.2%, PC: 55.3%; $p<0.01$) and in the multivariable analysis (PE *vs.* PC; OR=9.9, 95% CI=4.5-21.7; $p<0.01$) (GC *vs.* PC; OR=4.7, 95% CI=2.9-7.5; $p<0.01$).

There was a trend towards a higher risk of severe toxicity among patients with poor PS in univariable analyses (PS 0-1: 75.1%, PS 2: 82.6%; $p=0.096$). In the multivariable analyses, adjusting for baseline characteristics, poor PS was an independent predictive factor for toxicity (PS 2 *vs.* PS 0-1; OR=1.8, 95% CI=1.0-3.2; $p=0.046$). No other baseline characteristics were significantly associated with severe toxicity.

*Timing of severe toxicity.* Among patients experiencing severe toxicity, 249 (57.5%) first experienced severe toxicity

after the first course, 109 (25.2%) after the second, 54 (12.5%) after the third, and 18 (4.2%) after the fourth course (Figure 4). Despite delays and/or dose reductions due to severe toxicity, approximately half of the patients also experienced severe toxicity after the subsequent course, and the proportions were similar independent of when they first experienced severe toxicity (51.0%, 56.0% and 42.6% respectively; $p$=0.65) (Figure 4).

*Associations between baseline characteristics and timing of severe toxicity*. Patients on the GC arm who experienced severe toxicity were more likely to experience their first severe toxicity after the first course (GC: 69.8% after the first course *vs*. 30.2% after course 2-4, PC: 48.7% *vs*. 51.3%, PE: 51.0% *vs*. 49.0%; $p$<0.010) (Table I).

Despite the initial dose-reduction in the PEG trial, patients at the age of ≥75 years had a higher risk of experiencing severe toxicity after the first course (≥75: 70.5%, <75: 55.8%; $p$=0.032), though this difference was not statistically significant in the multivariable analysis (≥75 *vs*. <75; OR=1.7, 95% CI=0.9-3.0; $p$=0.102). No other baseline characteristics were associated with the timing of severe toxicity.

*Survival*. At the time of analyses, 452 of the included patients (79.4%) were dead. Patients experiencing severe toxicity had longer median overall survival than others (14.7 *vs*. 11.3 months; $p$=0.011), mainly due to a large numerical difference among the HAST patients (23.6 *vs*. 12.8 months; $p$=0.193). Patients who first experienced severe toxicity after the second course or later had significantly longer median overall survival than those who experienced severe toxicity after the first course (16.4 *vs*. 9.6 months; $p$=0.003) (Figure 5). The difference was statistically significant for PEG patients (9.7 *vs*. 7.2 months; $p$=0.046), but not for HAST patients (24.7 *vs*. 20.4 months; $p$=0.302). However, the differences were not statistically significant in the multivariable analyses (severe toxicity *vs*. no severe toxicity; HR=0.92; $p$=0.552) (severe toxicity after the first course *vs*. later; HR=1.22; $p$=0.110).

## Discussion

In this analysis of results from two randomized trials including lung cancer patients, we found that the majority (76%) of patients experienced severe toxicity from chemotherapy. Most of these patients (57.5%) first experienced toxicity after the first course, and despite dose-adjustments and delays, half of the patients also experienced severe toxicity after the subsequent course. Poor PS (PS 2) was the only independent predictive factor for severe toxicity during the treatment period, while chemotherapy regimen was the only predictor of when during the treatment period the first severe toxicity occurred; patients who received gemcitabine plus carboplatin experienced more toxicity after the first course than other patients. Interestingly, patients experiencing severe toxicity had a numerically longer median overall survival than other patients.

The rate of severe toxicity in this study was comparable to other studies of the platinum-doublets administered in our cohort (8-12), and also in another first-line study of pemetrexed-platinum, the gemcitabine-combination caused more severe toxicity (9). Furthermore, PS has also been identified as an independent predictive factor for severe toxicity in other studies (13).

All other studies investigating timing of chemotherapy toxicity also report that the first episode of severe toxicity most frequently occurred after the first course, though most studies only report haematological toxicity (4, 14-18). Only two studies investigated the frequency of severe toxicity after subsequent courses. In both of these studies, the proportion declined after the following course, and was within the same range as in our study; 46% in patients without dose-modification and 35% in patients with dose-modifications, although only 61 out of 200 patients were included in this analysis in the study by Extermann et al. (14). In contrast to our study, Culakova et al. reported that the frequency of severe toxicity declined for each course (4, 14). These studies are, however, not necessarily fully comparable due to major differences in types of cancer, treatment schedules, routines for dose modifications and classification of toxicity.

Whether both advanced NSCLC and LD SCLC patients should have been included can be debated, since treatment toxicity may be more acceptable for patients receiving potentially curative treatment. However, the results clearly indicate that the pattern of timing of toxicity varies for each chemotherapy regimen. The external validity of patients found eligible for randomized trials might be limited, since study cohorts in general are younger and more fit than many patients seen in the clinic (18, 19). On the other hand, the prospective data collection is a strength in our study, and this is one of a few studies reporting the timing of both haematological and non-haematological toxicity. The variation in chemotherapy doses for elderly and dose adjustments are other potential limitations, though our experience and population-based studies suggest that there are also variations in clinical practice (20-22). Finally, growth factors were not recommended in Norway when the trials were conducted, and we have not adjusted for transfusion of red blood cells or platelets.

Chemotherapy-related toxicity is associated with considerable morbidity, mortality and costs for the health care system (2), and numerous studies of risk factors have been conducted. Old age, poor performance status (PS), advanced disease stage, severe comorbidity and low body skeletal muscle mass are some of the characteristics most commonly found to be associated with a higher risk of severe toxicity (13, 14, 23-

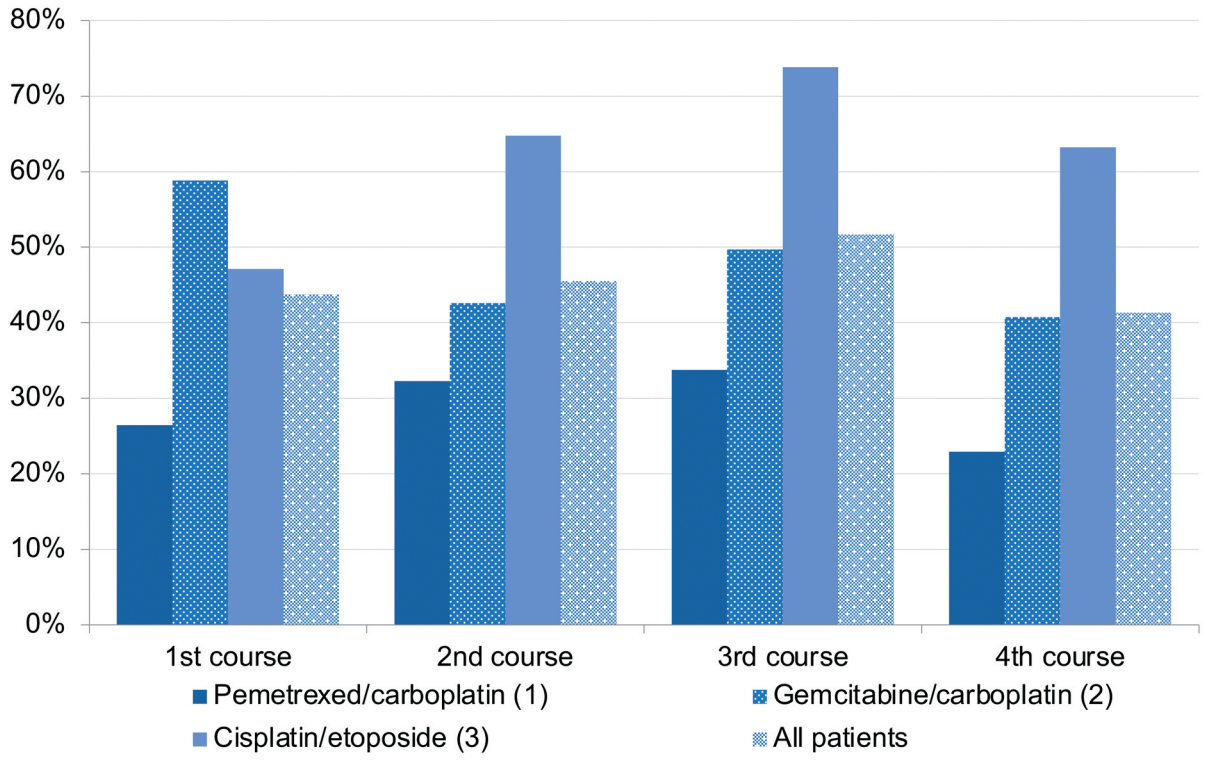


Figure 2. *Proportion of patients with severe toxicity after each course split for treatment arm.*

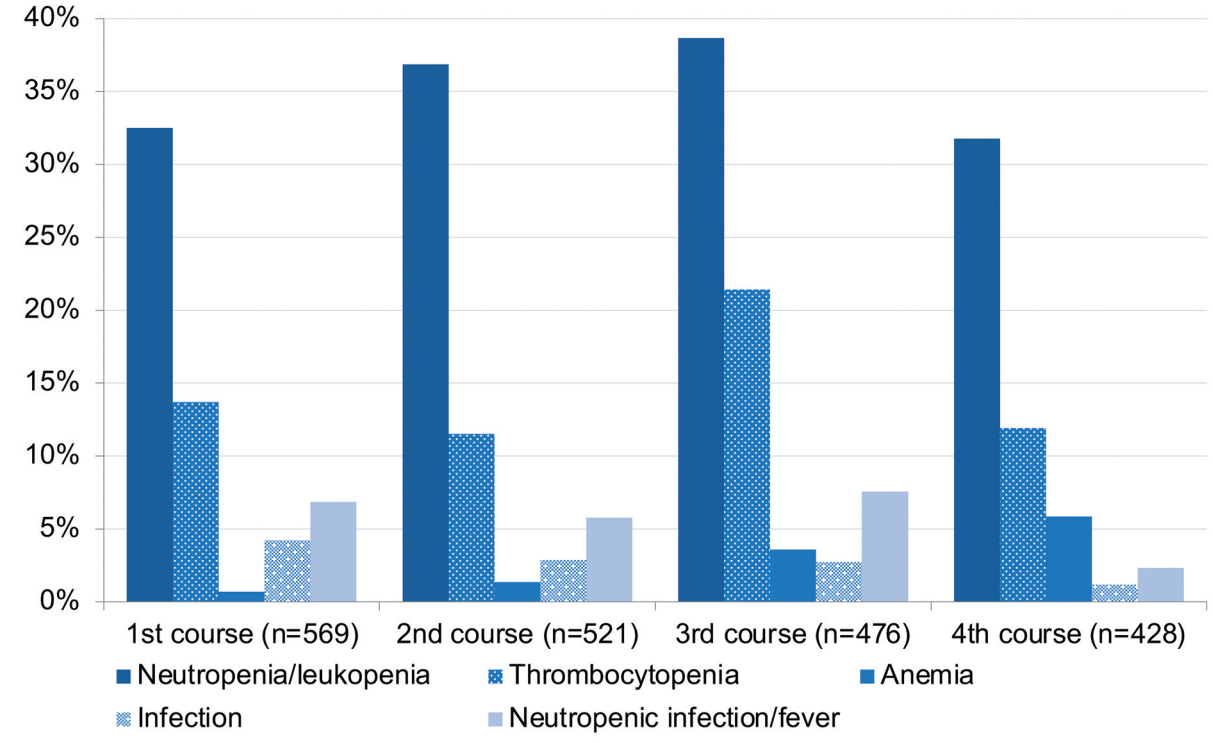


Figure 3. *Types of severe toxicities after each chemotherapy course with respective frequencies.*

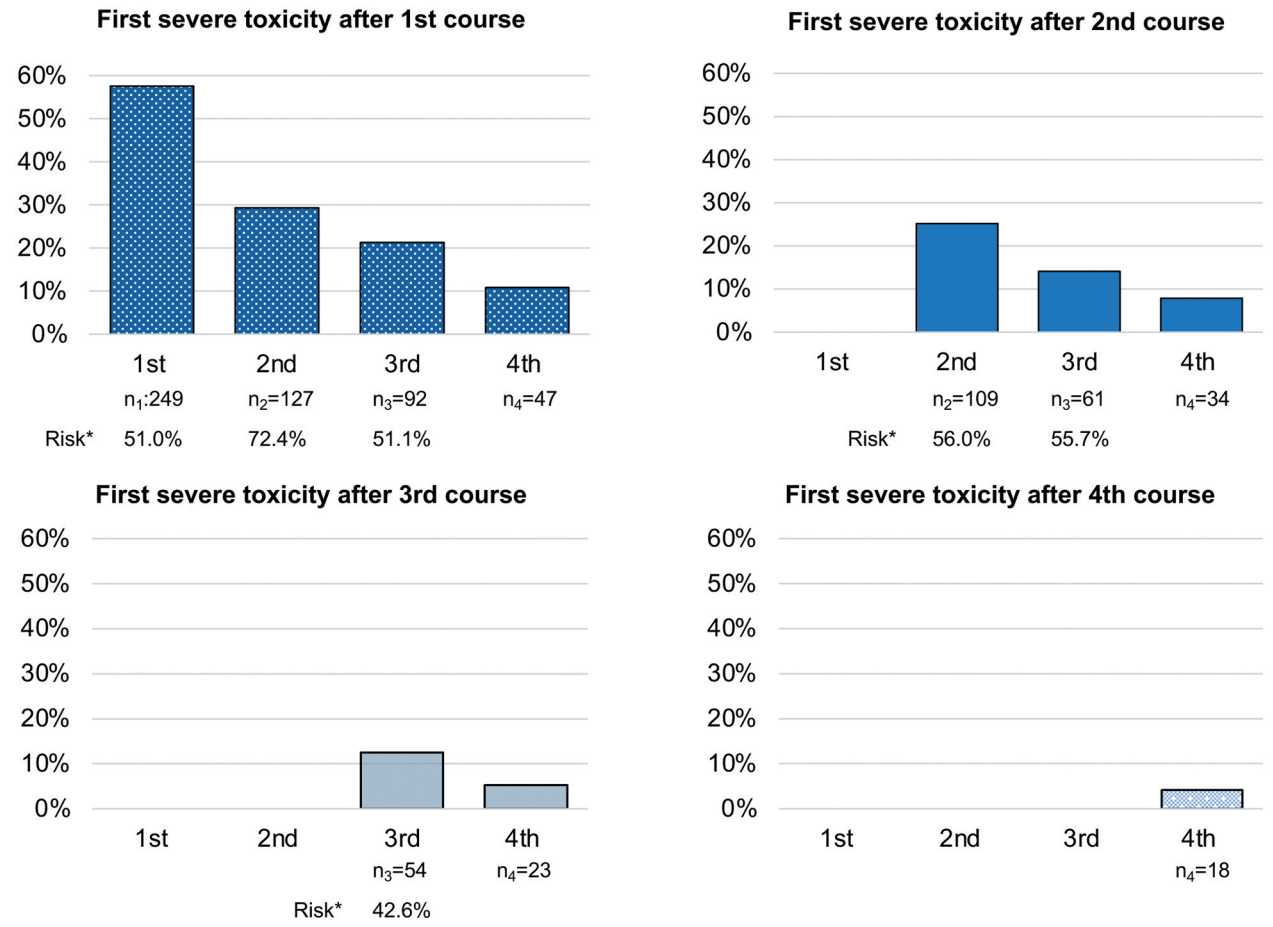


Figure 4. *Proportion of patients with repeated severe toxicity after subsequent courses – split for when the first severe toxicity occurred.*

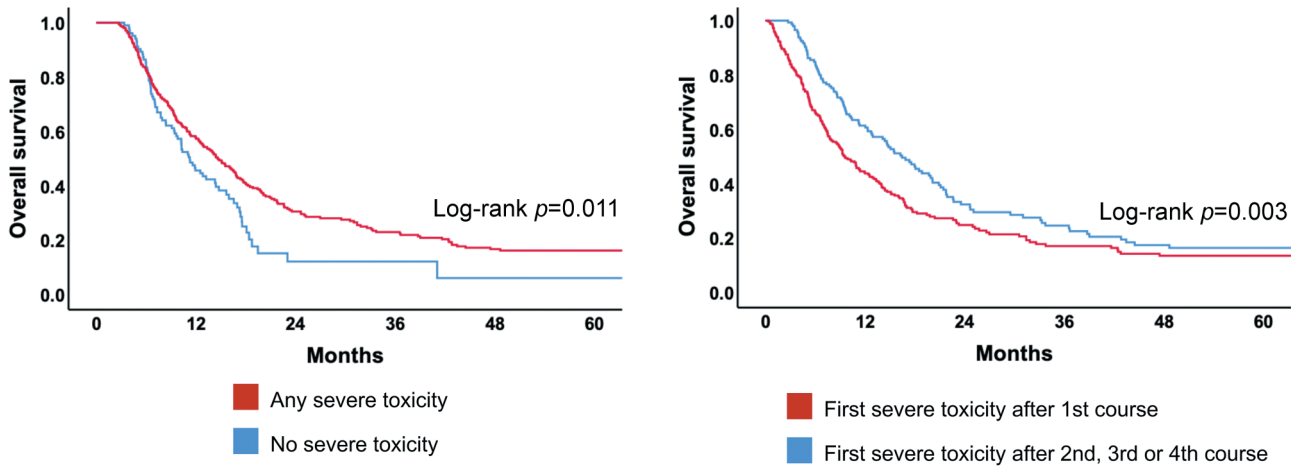


Figure 5. *Overall survival compared using Kaplan-Meier method and logrank test.*

26), and several models predicting chemotherapy toxicity have been suggested (15-18, 23). However, it remains unclear how these results should be implemented at the clinic. Many studies are retrospective analyses, often including participants with a wide range of patient and disease characteristics and none were designed to assess whether lowering the chemotherapy doses reduces the efficacy of the treatment. The latter is essential, since both ours and other studies indicate that patients experiencing severe chemotherapy toxicity live longer than those who do not (27, 28).

Most chemotherapy doses are calculated according to body surface area (BSA), which is estimated using the formula developed by Dubois and Dubois in 1916, based on a study of only nine subjects. This crude method does not account for differences in body composition and distribution or elimination of drugs. Several efforts have been made to develop better tools for individualizing chemotherapy doses, but only calculation of carboplatin dose based on glomerular filtration rate (GFR) and estimated drug concentration over time (AUC) is routinely used.

Despite the introduction of targeted therapies and immunotherapy, cytotoxic chemotherapy remains an essential therapy for many cancer patients, including lung cancer patients. Thus, continued efforts aiming at individualizing chemotherapy doses in order to reduce toxicity while maintaining efficacy, are most welcome. We believe that our study shows that such efforts should include data showing on which point during a treatment period severe toxicity occurs, what kind of toxicity occurs at each timepoint, the impact of dose-reductions and delays, as well as the benefit of supportive measures. Furthermore, results of studies of some regimens are not necessarily valid for other chemotherapies.

In conclusion, we found that a large proportion of lung cancer patients experience severe treatment toxicity after the first chemotherapy course, but many patients also experience treatment toxicity for the first time after the second, third and fourth course. This pattern varied between the three chemotherapy regimens administered in our study cohort. Poor PS was the only predictor of overall severe toxicity, and there were no predictors of timing of severe toxicity. Patients who experienced severe toxicity had a longer overall survival than those who did not.

## Conflicts of Interest

The Authors report no conflicts of interest.

## Authors' Contributions

KS and KAJ were responsible for analysis and preparation of results for publication under supervision of TOH. BHG conceived and designed the analysis. KS, KAJ, BHG and TOH wrote the paper.

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## References

1 Kristensen A, Solheim TS, Flotten O and Gronberg BH: Associations between hematologic toxicity and health-related quality of life during first-line chemotherapy in advanced non-small-cell lung cancer: A pooled analysis of two randomized trials. Acta Oncol *57(11)*: 1574-1579, 2018. PMID: 30074418. DOI: 10.1080/0284186X.2018.1492151

2 Kuderer NM, Dale DC, Crawford J, Cosler LE and Lyman GH: Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer *106(10)*: 2258-2266, 2006. PMID: 16575919. DOI: 10.1002/cncr.21847

3 Wang Y, Probin V and Zhou D: Cancer therapy-induced residual bone marrow injury-mechanisms of induction and implication for therapy. Curr Cancer Ther Rev *2(3)*: 271-279, 2006. PMID: 19936034. DOI: 10.2174/157339406777934717

4 Culakova E, Thota R, Poniewierski MS, Kuderer NM, Wogu AF, Dale DC, Crawford J and Lyman GH: Patterns of chemotherapy-associated toxicity and supportive care in us oncology practice: A nationwide prospective cohort study. Cancer Med *3(2)*: 434-444, 2014. PMID: 24706592. DOI: 10.1002/cam4.200

5 Gronberg BH, Bremnes RM, Flotten O, Amundsen T, Brunsvig PF, Hjelde HH, Kaasa S, von Plessen C, Stornes F, Tollali T, Wammer F, Aasebo U and Sundstrom S: Phase iii study by the norwegian lung cancer study group: Pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol *27(19)*: 3217-3224, 2009. PMID: 19433683. DOI: 10.1200/JCO.2008.20.9114

6 Halvorsen TO, Sundstrom S, Flotten O, Brustugun OT, Brunsvig P, Aasebo U, Bremnes RM, Kaasa S and Gronberg BH: Comorbidity and outcomes of concurrent chemo- and radiotherapy in limited disease small cell lung cancer. Acta Oncol *55(11)*: 1349-1354, 2016. PMID: 27549509. DOI: 10.1080/0284186X.2016.1201216

7 Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN and Rubin P: Ctcae v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol *13(3)*: 176-181, 2003. PMID: 12903007. DOI: 10.1016/S1053-4296(03)00031-6

8 Sederholm C, Hillerdal G, Lamberg K, Kolbeck K, Dufmats M, Westberg R and Gawande SR: Phase iii trial of gemcitabine plus carboplatin *versus* single-agent gemcitabine in the treatment of locally advanced or metastatic non-small-cell lung cancer: The swedish lung cancer study group. J Clin Oncol *23(33)*: 8380-8388, 2005. PMID: 16293868. DOI: 10.1200/JCO.2005.01.2781

9 Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis F, Simms L, Sugarman KP and Gandara D: Phase iii study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with

advanced-stage non-small-cell lung cancer. J Clin Oncol *26(21)*: 3543-3551, 2008. PMID: 18506025. DOI: 10.1200/JCO.2007.15.0375

10 Rodrigues-Pereira J, Kim JH, Magallanes M, Lee DH, Wang J, Ganju V, Martinez-Barrera L, Barraclough H, van Kooten M and Orlando M: A randomized phase 3 trial comparing pemetrexed/carboplatin and docetaxel/carboplatin as first-line treatment for advanced, nonsquamous non-small cell lung cancer. J Thorac Oncol *6(11)*: 1907-1914, 2011. PMID: 22005471. DOI: 10.1097/JTO.0b013e318226b5fa

11 Faivre-Finn C, Snee M, Ashcroft L, Appel W, Barlesi F, Bhatnagar A, Bezjak A, Cardenal F, Fournel P, Harden S, Le Pechoux C, McMenemin R, Mohammed N, O'Brien M, Pantarotto J, Surmont V, Van Meerbeeck JP, Woll PJ, Lorigan P, Blackhall F and Team CS: Concurrent once-daily *versus* twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (convert): An open-label, phase 3, randomised, superiority trial. Lancet Oncol *18(8)*: 1116-1125, 2017. PMID: 28642008. DOI: 10.1016/S1470-2045(17)30318-2

12 Berghmans T, Scherpereel A, Meert AP, Giner V, Lecomte J, Lafitte JJ, Leclercq N, Paesmans M, Sculier JP and European Lung Cancer Working P: A phase iii randomized study comparing a chemotherapy with cisplatin and etoposide to a etoposide regimen without cisplatin for patients with extensive small-cell lung cancer. Front Oncol *7:* 217, 2017. PMID: 28975084. DOI: 10.3389/fonc.2017.00217

13 Phaibulvatanapong E, Srinonprasert V and Ithimakin S: Risk factors for chemotherapy-related toxicity and adverse events in elderly thai cancer patients: A prospective study. Oncology *94(3)*: 149-160, 2018. PMID: 29212082. DOI: 10.1159/000485078

14 Extermann M, Reich RR and Sehovic M: Chemotoxicity recurrence in older patients: Risk factors and effectiveness of preventive strategies-a prospective study. Cancer *121(17)*: 2984-2992, 2015. PMID: 26033177. DOI: 10.1002/cncr.29423

15 Hosmer W, Malin J and Wong M: Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer. Support Care Cancer *19(3)*: 333-341, 2011. PMID: 20179995. DOI: 10.1007/s00520-010-0821-1

16 Lyman GH, Kuderer NM, Crawford J, Wolff DA, Culakova E, Poniewierski MS and Dale DC: Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. Cancer *117(9)*: 1917-1927, 2011. PMID: 21509769. DOI: 10.1002/cncr.25691

17 Schwenkglenks M, Bendall KL, Pfeil AM, Szabo Z and Pettengell R: External validation of a risk model of febrile neutropenia occurrence in patients with non-hodgkin lymphoma. Leuk Lymphoma *54(11)*: 2426-2432, 2013. PMID: 23452152. DOI: 10.3109/10428194.2013.780287

18 Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, Levine RM, Lubiner ET, Reyes P, Schreiber FJ, 3rd and Balducci L: Predicting the risk of chemotherapy toxicity in older patients: The chemotherapy risk assessment scale for high-age patients (crash) score. Cancer *118(13)*: 3377-3386, 2012. PMID: 22072065. DOI: 10.1002/cncr.26646

19 Martin F and Susan SM: Improving the external validity of clinical trials: The case of multiple chronic conditions. J Comorb *3(Spec Issue)*: 30-35, 2013. PMID: 29090144. DOI: 10.15256/joc.2013.3.27

20 Kehl KL, Hassett MJ and Schrag D: Patterns of care for older patients with stage iv non-small cell lung cancer in the immunotherapy era. Cancer Med *9(6)*: 2019-2029, 2020. PMID: 31989786. DOI: 10.1002/cam4.2854

21 Blom EF, Ten Haaf K, Arenberg DA and de Koning HJ: Disparities in receiving guideline-concordant treatment for lung cancer in the united states. Ann Am Thorac Soc *17(2)*: 186-194, 2020. PMID: 31672025. DOI: 10.1513/AnnalsATS.201901-094OC

22 Gajra A, Klepin HD, Feng T, Tew WP, Mohile SG, Owusu C, Gross CP, Lichtman SM, Wildes TM, Chapman AE, Dotan E, Katheria V, Zavala L, Akiba C, Hurria A, Cancer and Aging Research G: Predictors of chemotherapy dose reduction at first cycle in patients age 65 years and older with solid tumors. J Geriatr Oncol *6(2)*: 133-140, 2015. PMID: 25666905. DOI: 10.1016/j.jgo.2014.12.002

23 Nishijima TF, Deal AM, Williams GR, Sanoff HK, Nyrop KA and Muss HB: Chemotherapy toxicity risk score for treatment decisions in older adults with advanced solid tumors. Oncologist *23(5)*: 573-579, 2018. PMID: 29371477. DOI: 10.1634/theoncologist.2017-0559

24 Kale MS, Mhango G, Gomez JE, Sigel K, Smith CB, Bonomi M and Wisnivesky JP: Treatment toxicity in elderly patients with advanced non-small cell lung cancer. Am J Clin Oncol *40(5)*: 470-476, 2017. PMID: 25784564. DOI: 10.1097/COC.0000000000000188

25 Lyman GH, Abella E and Pettengell R: Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. Crit Rev Oncol Hematol *90(3)*: 190-199, 2014. PMID: 24434034. DOI: 10.1016/j.critrevonc.2013.12.006

26 Sjoblom B, Gronberg BH, Benth JS, Baracos VE, Flotten O, Hjermstad MJ, Aass N and Jordhoy M: Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. Lung Cancer *90(1)*: 85-91, 2015. PMID: 26198373. DOI: 10.1016/j.lungcan.2015.07.001

27 Di Maio M, Gridelli C, Gallo C, Shepherd F, Piantedosi FV, Cigolari S, Manzione L, Illiano A, Barbera S, Robbiati SF, Frontini L, Piazza E, Ianniello GP, Veltri E, Castiglione F, Rosetti F, Gebbia V, Seymour L, Chiodini P and Perrone F: Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: A pooled analysis of three randomised trials. Lancet Oncol *6(9)*: 669-677, 2005. PMID: 16129367. DOI: 10.1016/S1470-2045(05)70255-2

28 Kishida Y, Kawahara M, Teramukai S, Kubota K, Komuta K, Minato K, Mio T, Fujita Y, Yonei T, Nakano K, Tsuboi M, Shibata K, Atagi S, Kawaguchi T, Furuse K and Fukushima M: Chemotherapy-induced neutropenia as a prognostic factor in advanced non-small-cell lung cancer: Results from japan multinational trial organization lc00-03. Br J Cancer *101(9)*: 1537-1542, 2009. PMID: 19862000. DOI: 10.1038/sj.bjc.6605348

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