# The Importance of Dose Intensity When Administering Cytotoxic Chemotherapy in NSCLC—A Matter as Actual Now as in the Past


### *Authors:*

Cornelia Nitipir, Cristina Orlov-Slavu, Mihaela Olaru, Andreea Parosanu, Ana-Maria Popa, Cristian Iaciu, Bogdan Catalin Popescu, Maria Alexandra Barbu, Cristina Pirlog, Valentin Calu, Andreea Catarina Popescu, Dragos Bumbacea, Cristian Paleru, Iulian Slavu, Lucian Alecu



*Date Submitted:* 2020-12-17

*Keywords:* chemotherapy, administration, dose intensity



*Abstract:*

Lung cancer, as the leading cause of death in oncology is one of the most challenging diseases nowadays. Even after the implementation of checkpoint inhibitors and targeted therapy as a standard of therapy for metastatic disease, the chemotherapy backbone remains essential in the treatment of these patients. This study aimed to evaluate how administration particularities in chemotherapy and toxicity management can influence the outcome. We conducted a retrospective single-institution study, at Elias University Emergency Hospital, Bucharest, Romania, between 2014 and 2018, in a heterogeneous patient population with metastatic non-small cell lung cancer that received combination chemotherapy. The inclusion criteria for this trial were—histological proof of non-small cell lung cancer (NSCLC), stage IV disease, ECOG (Eastern Cooperative Oncology Group) performance status of a maximum of two, treatment with cytotoxic chemotherapy for at least four courses (patients with fewer courses were excluded). All patients received combination chemotherapy. The main focus was on the effect of dose reduction and treatment delay on overall survival and progression-free survival. A total of 129 patients were enrolled. The response rate in the studied population was 69% and 62.8% had no toxicity greater than grade 2. Chemotherapy regimens used had the following distribution—paclitaxel + carboplatin 41.9%, paclitaxel + carboplatin + bevacizumab 12.4%, pemetrexed + carboplatin 12.4%, gemcitabine + carboplatin 26.4% and other regimens 7%. Mean PFS (Progression Free Survival) was 9.1 months and the mean OS (Overall Survival) was 14 months. OS was not significantly different in the treatment delay group versus the no delay one, $p < 0.25$ but dose- reduction significantly impacted OS, $p < 0.03$. Administration particularities, like febrile neutropenia prophylaxis, treatment of chemotherapy-related anemia, respecting the details of chemostability and preparation rules and emesis prophylaxis, were considered reasons for the good outcome. Details regarding cytotoxic chemotherapy administration remain of paramount importance for a good outcome and the benefit for survival they convey is crucial. Sometimes the benefit the patient derives from these details is comparable to the one newer therapies convey.



*Record Type:* Published Article

*Submitted To:* LAPSE (Living Archive for Process Systems Engineering)

| | |
|---|---|
| *Citation (overall record, always the latest version):* | LAPSE:2020.1211 |
| *Citation (this specific file, latest version):* | LAPSE:2020.1211-1 |
| *Citation (this specific file, this version):* | LAPSE:2020.1211-1v1 |

*DOI of Published Version:* https://doi.org/10.3390/pr8080936

processes

MDPI

Article

# The Importance of Dose Intensity When Administering Cytotoxic Chemotherapy in NSCLC—A Matter as Actual Now as in the Past

**Cornelia Nitipir [1,2], Cristina Orlov-Slavu [1,*], Mihaela Olaru [1], Andreea Parosanu [1], Ana-Maria Popa [1,2], Cristian Iaciu [1,2], Bogdan Catalin Popescu [1], Maria Alexandra Barbu [1,2], Cristina Pirlog [1], Valentin Calu [2,3], Andreea Catarina Popescu [2,4], Dragos Bumbacea [2,5], Cristian Paleru [2,6], Iulian Slavu [7] and Lucian Alecu [7]**

1 Clinic of Oncology, Elias University Emergency Hospital, 011461 Bucharest, Romania; nitipir2003@yahoo.com (C.N.); miha0611@yahoo.com (M.O.); aparosanu@yahoo.com (A.P.); amy.popa@yahoo.com (A.-M.P.); iaciu.cristian@yahoo.com (C.I.); bogdanpopescu87@yahoo.com (B.C.P.); m.barbu86@gmail.com (M.A.B.); florinacristina_grosu@yahoo.com (C.P.)
2 Faculty of Medicine, Carol Davila University of Medicine and Pharmacy, 020021 Bucharest, Romania; drcalu@yahoo.com (V.C.); andreea.catarina.popescu@gmail.com (A.C.P.); d.bumbacea@gmail.com (D.B.); cpaleru@gmail.com (C.P.)
3 Clinic of General Surgery, Elias University Emergency Hospital, 11468 Bucharest, Romania
4 Cardiology Department, Elias University Emergency Hospital, 011461 Bucharest, Romania
5 Pneumology Clinic, Elias University Emergency Hospital, 011461 Bucharest, Romania
6 Thoracic Surgery Clinic, Marius Nasta National Institute of Pneumology, 050152 Bucharest, Romania
7 Clinic of General Surgery, Agrippa Ionescu Emergency Hospital, 011365 Bucharest, Romania; iulian.slavu@yahoo.com (I.S.); lucianalecu@yahoo.com (L.A.)
* Correspondence: cristina.slavu@drd.umfcd.ro; Tel.: +40-7-4051-7966

Received: 19 July 2020; Accepted: 31 July 2020; Published: 4 August 2020


**Abstract:** Lung cancer, as the leading cause of death in oncology is one of the most challenging diseases nowadays. Even after the implementation of checkpoint inhibitors and targeted therapy as a standard of therapy for metastatic disease, the chemotherapy backbone remains essential in the treatment of these patients. This study aimed to evaluate how administration particularities in chemotherapy and toxicity management can influence the outcome. We conducted a retrospective single-institution study, at Elias University Emergency Hospital, Bucharest, Romania, between 2014 and 2018, in a heterogeneous patient population with metastatic non-small cell lung cancer that received combination chemotherapy. The inclusion criteria for this trial were—histological proof of non-small cell lung cancer (NSCLC), stage IV disease, ECOG (Eastern Cooperative Oncology Group) performance status of a maximum of two, treatment with cytotoxic chemotherapy for at least four courses (patients with fewer courses were excluded). All patients received combination chemotherapy. The main focus was on the effect of dose reduction and treatment delay on overall survival and progression-free survival. A total of 129 patients were enrolled. The response rate in the studied population was 69% and 62.8% had no toxicity greater than grade 2. Chemotherapy regimens used had the following distribution—paclitaxel + carboplatin 41.9%, paclitaxel + carboplatin + bevacizumab 12.4%, pemetrexed + carboplatin 12.4%, gemcitabine + carboplatin 26.4% and other regimens 7%. Mean PFS (Progression Free Survival) was 9.1 months and the mean OS (Overall Survival) was 14 months. OS was not significantly different in the treatment delay group versus the no delay one, $p < 0.25$ but dose- reduction significantly impacted OS, $p < 0.03$. Administration particularities, like febrile neutropenia prophylaxis, treatment of chemotherapy-related anemia, respecting the details of chemostability and preparation rules and emesis prophylaxis, were considered reasons for the good outcome. Details regarding cytotoxic chemotherapy administration remain of paramount importance for a good outcome and the benefit for survival they convey is crucial. Sometimes the benefit the patient derives from these details is comparable to the one newer therapies convey.

**Keywords:** dose intensity; administration; chemotherapy

## 1. Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of death in oncology [1].

Although recent developments have changed how the oncology community perceives this disease and longer survival has been achieved both with immunotherapy and targeted therapies, the chemotherapy backbone is still necessary for most patients in first or subsequent lines of therapy. The present paper is a mere attempt to underline the importance of details when administering classical cytotoxic chemotherapy in metastatic NSCLC and focuses on adequate dose intensity, following the rules of preparation and maintaining compound stability and their relation to the patients' outcome. Chemotherapy agents used in this trial included—paclitaxel, pemetrexed, gemcitabine, carboplatin, cisplatin and docetaxel. Some regimens also included bevacizumab, a monoclonal antibody. Other matters such as chemostability, preparation rules, adverse reactions prophylaxis and treatment have also been discussed and the particular approach of our center has been illustrated.

## 2. Materials and Methods

The present paper is a retrospective study that included all patients with metastatic non-small cell lung cancer that received combination chemotherapy at Elias University Emergency Hospital, Bucharest, Romania, between 2014 and 2018. The research was undertaken with the approval of the Elias University Hospital Ethics Committee approval (identification code 3336, date of approval 30 July 2020) The inclusion criteria for this trial were—histological proof of NSCLC, stage IV disease, ECOG performance status of maximum 2, treatment with cytotoxic chemotherapy for at least 4 courses (patients with fewer courses were excluded). We also excluded patients with ALK rearrangement or EGFR mutations who received targeted therapy. The most important variables were reported in a dichotomic manner—presence or absence of grade 2 or greater toxicities, dose reduction, whether the patient had any treatment delay. The percentage of the dose reduction, its duration and the use of granulocyte-colony stimulating factor (G-CSF) were also reported. The present study has the approval of the Elias University Emergency Hospital ethical committee.

To report dose reduction, the standard dose intensity and the relative dose intensity were calculated at first, using the following formulas [2]:

$$\text{Dose intensity} = \text{chemotherapy dose delivered per time (mg/m}^2\text{ of body surface/week)}$$

$$\text{Relative dose intensity} = \text{dose intensity of chemotherapy delivered/standard dose intensity.}$$

The response was defined as anything other than progression (it included stationary disease) and was assessed using only imaging criteria that respected RECIST 1.1. Patients underwent imaging every 3–4 months during treatment [3].

Toxicities were recorded from patients charts and graded using CTCAE version 4 [4].

Dose intensity was conventionally defined as the dosage of the chemotherapy agent per unit of body mass (square meters) per time unit usually measured in weeks. All the included patients received combination regimens, so the authors reported the dose intensity as a sum. The regimens used included—paclitaxel 200 mg/m$^2$ + carboplatin AUC = 6 q3w (every three weeks), paclitaxel 200 mg/m$^2$ + carboplatin AUC = 6 + bevacizumab 15mg/m$^2$ q3w, pemetrexed 500 mg/m$^2$ + carboplatin AUC = 6 q3w, gemcitabine 1000 mg/m$^2$ days 1, 8, 15 + carboplatin AUC = 4.5 every four weeks (q4w) as illustrated in Table 1. Regimens classified as other were—gemcitabine 1250 mg/m$^2$ day 1, 8 + cisplatin 80 mg/$^2$ q3w and docetaxel 75 mg/m$^2$+ cisplatin 75 mg/m$^2$ q3w.

**Table 1.** Regimens used for the studied population.

| Regimen | Administration |
|---|---|
| paclitaxel 200 mg/m$^2$ + carboplatin AUC = 6 | q3w |
| paclitaxel 200 mg/m$^2$ + carboplatin AUC = 6 + bevacizumab 15 mg/m$^2$ | q3w |
| pemetrexed 500 mg/m$^2$ + carboplatin AUC = 6 | q3w |
| gemcitabine 1000 mg/m$^2$ +carboplatin AUC = 4.5 | gemcitabine days 1, 8, 15, whole regimen q4w |
| gemcitabine 1250 mg/m$^2$ day 1, 8 + cisplatin 80 mg/$^2$ | gemcitabine days 1, 8 whole regimen q3w |
| docetaxel 75 mg/m$^2$+ cisplatin 75 mg/m$^2$ | q3w |

Statistical analysis was performed using IMB SPSS version 20. Progression-free survival (PFS) and overall survival (OS) were compared in the dose reduction subgroup vs. no dose reduction subgroup and the treatment delay subgroup vs. the non- treatment delay one using the Kaplan Meier method and statistical significance was measured with the log-rank test.

## 3. Results

A number of 129 patients were included. The mean age was 62 (range 29–80, SD = 9.36), 51.93% were female patients. The study included 28.7% of patients with squamous carcinoma (n = 37), 68.2% with adenocarcinoma (n = 88) and 3.1% with other subtypes (n = 4), such as large cell or sarcomatoid carcinoma. Chemotherapy regimens used had the following distribution—paclitaxel + carboplatin 41.9%, paclitaxel + carboplatin + bevacizumab 12.4%, pemetrexed + carboplatin 12.4%, gemcitabine + carboplatin 26.4% and other regimens 7%. The response rate in the studied population was 69% (with most 41.9%, having stable disease). 62.8% (n = 81) had no toxicity greater than grade 2. 14% of the patients (n = 18) had dose reduction. The maximum admitted dose reduction was 75% (in 5.42% of the patients). The mean dose reduction was 81.11%. An important part of the patients received primary prophylaxis for febrile neutropenia, with 45.5% receiving filgrastim and 5.4% receiving pegfilgrastim up-front. Peg filgrastim as secondary prophylaxis was used in 6.9% of the patients. The characteristics of the patients are described in detail in Table 2.

**Table 2.** Patients and their characteristics.

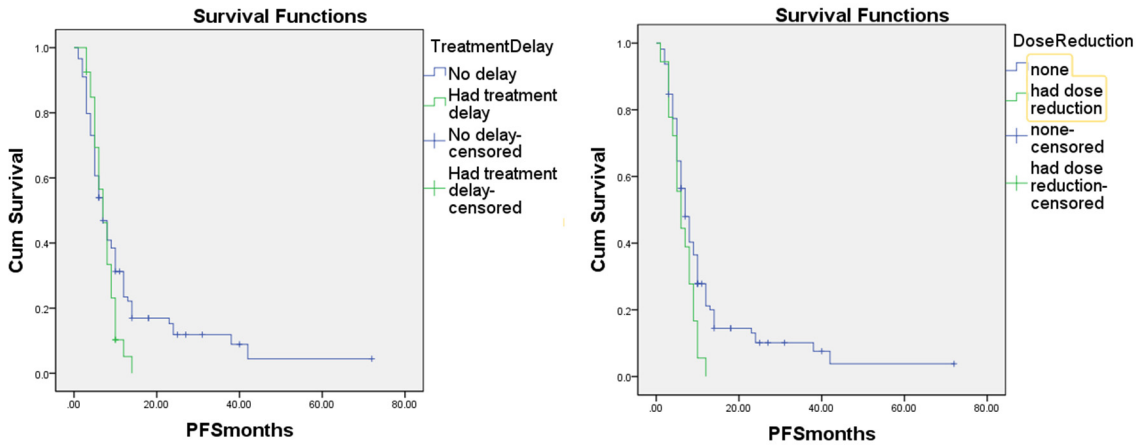
| Characteristics | N (%) |
|---|---|
| **Gender** | |
| Male | 62 (48.07%) |
| Female | 67 (51.93%) |
| **Age** | |
| Mean | 62 |
| Range | (29–80) |
| **Histology** | |
| Squamous cell carcinoma | 37 (28.7%) |
| ADK | 88 (68.2%) |
| Other | 4 (3.1%) |
| **Proportion of chemotherapy regimens** | |
| paclitaxel + carboplatin | 54 (41.9%) |
| paclitaxel + carboplatin + bevacizumab | 16 (12.4%) |
| pemetrexed + carboplatin | 16 (12.4%) |
| gemcitabine + carboplatin | 34 (26.4%) |
| Other | 9 (7%) |

**Table 2.** *Cont.*

| Characteristics | N (%) |
|---|---|
| **Toxicity** | |
| No toxicity | 21 (16.27%) |
| Grade 1 | 26 (20.15%) |
| Grade 2 | 34 (26.35%) |
| Over Grade 2 | 48 (37.20%) |
| **Type of toxicity over grade 2** | |
| Hematological | 40 (31.8%) |
| Non-hematological (deafness, peripheral neuropathy, pain) | 8 (6.2%) |
| **Dose reduction** | |
| 75% dose reduction | 7 (5.42%) |
| dose reduction between 85% and 75% | 11 (8.57%) |

Cox regression analysis was used to identify the variables that affected survival. Only the presence of dose reduction, the delay of treatment and the presence of higher than grade 2 toxicity were correlated with worse survival. The correlation had statistical significance only for treatment delay, $p < 0.07$.

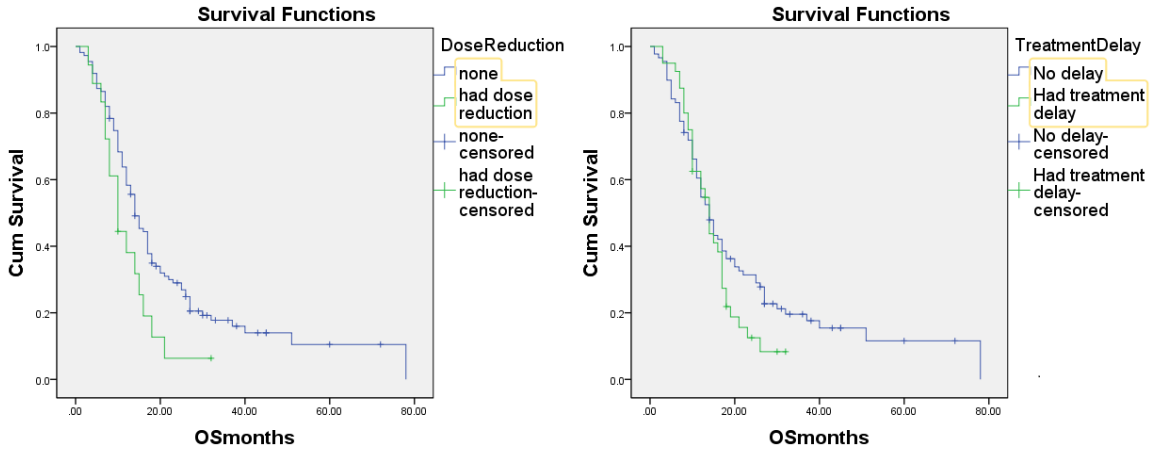
Mean PFS in the studied group was 9.1 months (SD = 9.09) with the following distribution—10.2 months in the paclitaxel + carboplatin group, 11.4 months in the paclitaxel+carboplatin+ bevacizumab group, 8.7 months in the pemetrexed + carboplatin, 5.6 months in the gemcitabine + cisplatin/carboplatin group and 6 months in the other regimens group. No statistically significant differences were observed when comparing PFS in the dose reduction and no-dose reduction groups, as Figure 1 shows, $p < 0.07$. The same was demonstrated when comparing PFS in patients who had treatment delay or not, $p < 0.09$ (Figure 1).




(**a**) (**b**)

**Figure 1.** Progression free survival in the (**a**) dose reduction subgroup vs. (**b**) no dose reduction and in the treatment delay group vs. no treatment delay.

Mean OS in the studied population was 14 months (SD = 13.01), with the following distribution—15.6 months in the paclitaxel + carboplatin group, 19.6 months in the paclitaxel + carboplatin + bevacizumab group, 10.8 months in the pemetrexed + carboplatin, 9.9 months in the gemcitabine + cisplatin/carboplatin group and 14.1 months in the other regimens group. OS was not significantly different in the treatment delay group versus the non-delay one, as Figure 2 shows, $p < 0.25$. However, significance for OS in the dose reduction group vs. the non-reduction group was observed, $p < 0.03$.




(**a**) (**b**)

**Figure 2.** Overall survival in the (**a**) dose reduction group versus (**b**) no dose reduction group and treatment delay versus no treatment delay group.

## 4. Discussion

The administration of the regimens has some particularities in our institution. First and foremost, the dosage was calculated for each presentation, instead of maintaining the dosage of the first administration if the patient's body mass area (BMA) had not dropped 10%, as some other centers do. When the patient developed chemotherapy-related anemia, supportive measures were adopted (like blood transfusion and the use of erythropoiesis-stimulating agents) but the maximum effort was made to maintain the 100% dosage [5,6].

The reason patients with fewer than 4 courses were excluded is that with short administration the effect of dose intensity on the patient outcome is minimal.

Primary prophylaxis of neutropenic fever was always preferred in the presence of intermediate overall risk after taking into consideration all the risk factors, such as liver dysfunction, kidney dysfunction, prior chemotherapy or radiation therapy and age over 65. Some of the patients with pemetrexed + carboplatin were, however, considered unfit for prophylaxis [7–10].

In the presence of grade 3–4 neutropenia with no fever, the first attitude was to administer filgrastim for a longer duration post-chemotherapy, rather than adjust chemotherapy dosage. When the treating physician considered necessary, peg-filgrastim was chosen. After administration patients were monitored with complete blood counts after seven and fourteen days. This helped the treating physician to understand the bone marrow dynamic and adjust the G-CSF administration. The patient was encouraged to assess complete blood counts in the vicinity of his or her home, for minimal discomfort. The results were usually transmitted to the general practitioner or a nurse in the institution [11].

The schedule was another important aspect. Patients were always instructed before treatment initiation about the importance of dose density and all the efforts were made to avoid delay. Even delay that has no relation to toxicity (legal holidays, other personal issues) were managed so that chemotherapy could be administered exactly when necessary. Drug interactions were also monitored. A complete list of concomitant medication was obtained at the time of the first presentation and interactions were checked. The patients were interrogated about any changes in the non-oncologic treatment regularly.

Chemostability and preparation rules were also of utmost importance. For each compound the rules were strictly followed. Paclitaxel or benzenepropanoic acid, classified as an antimicrotubule agent was always reconstituted using normal saline solution, in a concentration of 6 mg/mL and was administered in a non-containing di(2-ethylhexyl) phthalate (DEHP) bag through a filter of 0.22 microns, in 3 h. The duration of the administration is of paramount importance, preventing hypersensitivity reactions. Pemetrexed, an antifolate metabolite, also reconstituted with normal saline,

was usually administered in a 25 mg/mL concentration, in 10 min. Calcium containing dilutants were forbidden (such as Ringer lactate). Carboplatin or CBDCA, a platinum salt was always diluted in 5% glucose solution, at a concentration of 10 mg/mL. Aluminum containing needles, syringes or other administration devices were forbidden and administration time was 1 h. Gemcitabine, also known as gemcitabine hydrochloride or difluorodeoxycytidine or 2′,2′-difluorodeoxycytidine, was diluted using normal saline to a 38 mg/mL concentration, administration duration was 30 min.

All drugs were kept at optimal temperature and light before use, respecting manufacturer recommendations [12].

The regimens used in the studied patients had high emetogenic potential, either due to the presence of carboplatin AUC > 4 or to cisplatin. None of the patients, however, reported grade 2 or higher nausea or emesis. This was mainly due to the clinic antiemesis protocol that included both primary prophylactic medication as dexamethasone, 5-HT3 (hydroxytryptamine 3) receptor antagonists and sometimes olanzapine but also due to hydration administered with every course as detailed below [13].

In our clinic, attention to premedication is a continuous pensiveness. When administering paclitaxel and carboplatin, for example, premedication one day before includes—at least 1500 mL of hydration, steroids (dexamethasone 8 mg intravenously or oral equivalent), an antihistamine and histamine 2 receptor blockers (that acts as gastric mucosa protectant but also shares the antiallergic properties of loratadine). In the day of chemotherapy administration, steroids, antihistamines are re-administered together with at least 2500 mL of hydration are administered together. If the patient has received more than 5 courses of carboplatin, allergy testing is mandatory. In our clinic we use a prick cutaneous test that can be interpreted by the treating oncologist. The other regimens are also administered together with at least 2500 mL hydration. The use of diuretics can be necessary and is particularized for every patient. Nursing measures are also very well implemented (with attention to patient mobilization, advice not to keep feet down permanently during drug delivery). The nursing staff is well trained in identifying acute drug reactions and is always prompt in taking action [12].

Whenever necessary, evaluation of other specialties was requested (such as thoracic surgery, pneumology, cardiology, radiotherapy and palliative care) and all decisions for further treatment were taken in the multidisciplinary board [14,15].

The median OS observed in this study (14 months) was generally higher than the OS reported in phase III trials that established the studied regimens as standard in metastatic NSCLC. It has to be taken into consideration that all patients received combination chemotherapy and the synergic effect of the drugs had an important part to play in the proved efficacy.

The phase III trial by the Norwegian Lung Cancer Study Group compared pemetrexed+ carboplatin to gemcitabine + carboplatin in stage IIIB or IV NSCLC. The authors reported similar OS in the two groups (7.3 months for the first regimen vs. 7 months for the second one, $p = 0.63$). There were no differences in reported quality of life, either. Gemcitabine and carboplatin were, however associated with higher rates of neutropenia, leukopenia and thrombocytopenia [16].

Pemetrexed and carboplatin were better tolerated in our study as well, with lower rates of hematological toxicity, this being consistent with the literature [17–19].

Using cisplatin instead of carboplatin proved some benefit on OS but the median value was still lower than 14 months. The phase III trial by Scagliotti et al. compared two treatment arms (cisplatin and gemcitabine or cisplatin and pemetrexed for up to six cycles) in 1725 subjects with stage III B or IV NSCLC. The follow-up was only one year. Overall survival for patients randomly assigned to both arms was similar (median overall survival, 10.3 vs. 10.3 months; HR = 0.94, 95% CI: 0.84 to 1.05). Administration of cisplatin/pemetrexed proved better tolerability, a reduced need for supportive therapies and more convenient administration than cisplatin/gemcitabine [20].

In our study, 12.4% of patients used the addition of bevacizumab to paclitaxel and carboplatin. Alan S. et al., found that the addition of bevacizumab to a standard, platin-based, two-agent chemotherapy regimen provides a significant improvement in overall survival, response rate and progression-free

survival. In a randomized study conducted by the Eastern Cooperative Oncology Group (ECOG), 878 patients with recurrent or advanced non–small-cell lung cancer (stage III B or IV) were assigned to treatment with paclitaxel and carboplatin alone or with bevacizumab.

Median overall survival was of 12.3 months in the paclitaxel–carboplatin–bevacizumab arm, as compared with 10.3 months in the paclitaxel– carboplatin arm (OR, 0.79; 95% CI, 0.67–0.92; $p = 0.003$). At one year, the survival rate was higher in the group receiving bevacizumab (51% vs. 44%) [21].

When dealing with elderly patients, chemotherapy is frequently challenging due to comorbidities, drug interactions and age-related functional decline. As a consequence, dose intensity is frequently difficult to maintain. Relative dose intensity of less than 80% is suboptimal for tumor shrinkage [22,23].

According to our data, there was no difference in OS between the two age groups (under 65/over 65). 54/129 (41.8%) were patients over 65, with cytotoxic chemotherapy for at least 4 courses and the mean dose reduction was 81.11%. These findings confirm previous ones indicating that fit elderly patients with NSCLC can benefit as well as younger ones from chemotherapy at conventional dose intensity. The impact of personalized care during chemotherapy can be a valid explanation for the good tolerability of the regimens, even in the elderly population [24].

## 5. Conclusions

To summarize, we consider that all the aspects listed above are arguments for better tolerability and less chemotherapy dose reduction in metastatic NSCLC patients, and, as a consequence, for better survival. Even in the checkpoint inhibitors era, the chemotherapy backbone remains essential for the treatment of NSCLC. Details regarding cytotoxic chemotherapy administration remain of paramount importance for a good outcome and the benefit on survival they convey is crucial. Sometimes the benefit the patient derives from these details is comparable to the one newer therapies convey.

**Author Contributions:** Conceptualization: C.N. Methodology: C.N.; Software: C.O.-S.; Validation: C.P. (Cristian Paleru), D.B.; Formal analysis: A.-M.P., A.P.; Investigation: I.S., M.O. Resources; M.A.B., B.C.P., Data curation: C.O.-S., M.O., C.P. (Cristina Pirlog); Writing—original draft preparation: C.I. writing—review and editing: V.C., A.C.P.; visualization: V.C.; supervision: L.A. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2018**, *68*, 394–424. [CrossRef] [PubMed]
2. Lyman, G.H. Impact of Chemotherapy Dose Intensity on Cancer Patient Ourcomes. *J. Natl. Compr. Cancer Netw.* **2009**, *7*, 99–108. [CrossRef] [PubMed]
3. Eisenhauer, E.A.; Therasse, P.; Bogaerts, J.; Schwartz, L.H.; Sargent, D.; Ford, R.; Dancey, J.; Arbuck, S.; Gwyther, S.; Mooney, M.; et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur. J. Cancer* **2009**, *45*, 228–247. [CrossRef] [PubMed]
4. Common Terminology Criteria for Adverse Events (CTCAE) Version 4, published 28 May 2009 (v4.03: 14 June 2010) U.S. Department of Health and Human Services, NCI. Available online: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accessed on 5 May 2020).
5. Bokemeyer, C.F.; Aapro, M.S.; Courdi, A.; Foubert, J.; Link, H.; Österborg, A.; Repetto, L.; Soubeyran, P. EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. *Eur. J. Cancer* **2007**, *43*, 258–270. [CrossRef]
6. Aapro, M.S.; Link, H. September 2007 update on EORTC guidelines and anemia management with erythropoiesis-stimulating agents. *Oncologist* **2008**, *13* (Suppl. 3), 33–36. [CrossRef]

7. Pujol, J.L.; Breton, J.L.; Gervais, R.; Rebattu, P.; Depierre, A.; Morère, J.F.; Milleron, B.; Debieuvre, D.; Castéra, D.; Souquet, P.J.; et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastaic non-small cell lung cancer: A phase III study adressing the case for cisplatin. *Ann. Oncol.* **2005**, *16*, 602–610. [CrossRef]
8. Lymann, G.H.; Kunderer, N.M.; Crawford, J.; Wolff, D.A.; Culakova, E.; Poniewierski, M.S.; Dale, D.C. Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. *Cancer* **2011**, *117*, 1917–1927. [CrossRef]
9. Mazilu, L.; Stanculeanu, D.L.; Gheorghe, A.D.; Suceveanu, A.P.; Parepa, I.R.; Stoian, A.P.; Pop, C.S.; Bratu, O.; Suceveanu, A.I. Chemotherapy and other Factors Affecting Quality of Life in Non-Small Cell Lung Cancer (NSCLC) Patients. *Rev. Chim.* **2019**, *70*, 33–35. [CrossRef]
10. Aagaard, T.; Roen, A.; Reekie, J.; Daugaard, G.; Brown, P.D.; Specht, L.; Sengeløv, H.; Mocroft, A.; Lundgren, J.; Helleberg, M. Development and validation of a risk score for febrile neutropenia after chemotherapy in patients with cancer: The FENCS score. *JNCI Cancer Spectr.* **2018**, *2*, pky053. [CrossRef]
11. Lyman, G.H.; Abella, E.; Pettengell, R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. *Crit. Rev. Oncol. Hematol.* **2014**, *90*, 190–199. [CrossRef]
12. BC Cancer Agency. *Pharmacy Policy Number II-20: Guiding Principles for Chemotherapy Preparation Chart*; Cancer Agency: Vancouver, BC, Canada, 2007.
13. Grunberg, S.M.; Warr, D.; Gralla, R.J.; Rapoport, B.L.; Hesketh, P.J.; Jordan, K.; Espersen, B.T. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity- state of the art. *Support Care Cancer* **2011**, *19*, S43–S47. [CrossRef] [PubMed]
14. Mazilu, L.; Stanculeanu, D.L.; Gheorghe, A.D.; Voinea, F.; Suceveanu, A.P.; Pituru, S.; Diaconu, C.C.; Parepa, I.R.; Stoian, A.P.; Pop, C.S.; et al. Incidence of Chemotherapy-Induced Peripheral Neuropathy In Cancer Patients In Clinical Practice. *FARMACIA* **2019**, *67*, 472–476. [CrossRef]
15. Adrian, T.; Alecu, L.; Poiana, C.; Tomescu, L.; Slavu, I.; Tulin, R.; Pituru, S.; Orlov, C.; Jecan, R.; Cristian, B.; et al. Functional radical cervical dissection for differentiated thyroid cancer: The experience of a single center. *JMMS* **2018**, *5*, 278–283. [CrossRef]
16. Grønberg, B.H.; Bremnes, R.M.; Fløtten, Ø.; Amundsen, T.; Brunsvig, P.F.; Hjelde, H.H.; Kaasa, S.; von Plessen, C.; Stornes, F.; Tollåli, T.; et al. Phase III Study of the Norwegian Lung Cancer Study Group: Pemetrexed Plus carboplatin Compared With Gemcitabine Plus carboplatin As First Line Chemotherapy in Advanced NSCLC. *J. Clin. Oncol.* **2009**, *27*, 3217–3224. [CrossRef]
17. Le Chevalier, T.; Scagliotti, G.; Natale, R.; Danson, S.; Rosell, R.; Stahel, R.; Thomas, P.; Rudd, R.M.; Vansteenkiste, J.; Thatcher, N.; et al. Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens in advanced non-small-cell lung cancer: A meta-analysis of survival outcomes. *Lung Cancer* **2005**, *47*, 69–80. [CrossRef]
18. Wakelee, H.A.; Wang, W.; Schiller, J.H.; Langer, C.J.; Sandler, A.B.; Belani, C.P.; Johnson, D.H.; Eastern Cooperative Oncology Group. Survival differences by sex for patients with advanced non-small cell lung cancer on Eastern Cooperative Oncology Group trial 1594. *J. Thorac. Oncol.* **2006**, *1*, 441–446. [CrossRef]
19. Ohe, Y.; Ichinose, Y.; Nakagawa, K.; Tamura, T.; Kubota, K.; Yamamoto, N.; Adachi, S.; Nambu, Y.; Fujimoto, T.; Nishiwaki, Y.; et al. Efficacy and safety of two doses of pemetrexed supplemented with folic acid and vitamin B12 in previously treated patients with non-small cell lung cancer. *Clin. Cancer Res.* **2008**, *14*, 4206–4212. [CrossRef] [PubMed]
20. Scagliotti, G.V.; Parikh, P.; Von Pawel, J.; Biesma, B.; Vansteenkiste, J.; Manegold, C.; Serwatowski, P.; Gatzemeier, U.; Digumarti, R.; Zukin, M.; et al. 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.* **2008**, *26*, 3543–3551. [CrossRef]
21. Sandler, A.; Gray, R.; Perry, M.C.; Brahmer, J.; Schiller, J.H.; Dowlati, A.; Lilenbaum, R.; Johnson, D.H. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.* **2006**, *355*, 2542–2550. [CrossRef]
22. Skipper, H. *Data and Analysis Having to do with the Influence of Dose Intensity and Duration of Treatment (Single Drugs and Combination) on Lethal Toxicity and the Therapeutic Response of Experimental Neoplasm*; Southern Research Institute: Birmingam, UK, 1987.

23. Mazilu, L.; Stanculeanu, D.L.; Gheorghe, A.D.; Suceveanu, A.P.; Parepa, I.R.; Stoian Pantea, A.; Suceveanu, A.I. Clinical Impact of Association between Diabetes and Lung Cancer. *Rev. Chim.* **2019**, *70*, 1149–1151. [CrossRef]
24. Luciani, A.; Bertuzzi, C.; Ascione, G.; Di Gennaro, E.; Bozzoni, S.; Zonato, S.; Ferrari, D.; Foa, P. Dose intensity correlate with survival in elderly patients treated with chemotherapy for advanced non-small cell lung cancer. *Lung Cancer* **2009**, *66*, 94–96. [CrossRef] [PubMed]