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Project Title: **The Effect of Cisplatin Versus Carboplatin On Cancer Outcomes for Small Cell Lung Cancer Patients In Manitoba**

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Summary (250 words max single spaced):

Small cell lung cancer (SCLC) is associated with high rates of mortality and treatment involves chemotherapy. In non-small cell lung cancer, using the drug cisplatin results in superior response and survival compared to carboplatin, but causes more toxicity. Little research regarding this drug choice in SCLC exists, but the available studies suggest equivalent survival. Nevertheless, oncologists continue to use cisplatin preferentially.

Using the population-based Manitoba Cancer Registry, we identified SCLC cases diagnosed from 2004 to 2013 in Manitoba who were treated with chemotherapy and completed a retrospective chart review. Demographics, tumour response, and treatment toxicity were compared between cisplatin and carboplatin treated groups. Overall survival (OS) and progression free survival (PFS) were evaluated using multivariate Cox proportional hazard methods.

Of the 531 patients identified, 26.2% carboplatin and 73.8% received cisplatin in first line chemotherapy. More patients who received carboplatin had poor performance status (13.7% v 7.4%), elevated LDH (58.3% v 42.3%), and more extensive stage disease (69.8% v 54.1%), all $p<0.01$. Unadjusted median OS was 245 v 332 days for carboplatin and cisplatin. Multivariable adjusted analysis showed that cisplatin and carboplatin completers had equivalent hazard ratios for OS – 1.01 (0.78-1.31) and PFS – 0.95 (0.73-1.22). Those treated with carboplatin had significantly less neutropenia (57.6% v 74.7%), nephrotoxicity (2.9% v 13.5%), neurotoxicity (0.7% v 12.0%), and nausea/vomiting (28.1% v 42.6%) associated with treatment, all $p<0.01$.

Carboplatin appears to be an equally effective treatment option for SCLC, facilitating equivalent survival while avoiding toxicity. Clinicians may wish to reexamine their preference for cisplatin.

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The Effect of Cisplatin Versus Carboplatin On Cancer Outcomes for Small Cell Lung Cancer Patients In Manitoba

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Introduction:

Lung cancer is a major public health concern as it is the most common cause of cancer-related death worldwide. Worldwide, approximately 1.6 million new cases and 1.38 million deaths attributed to lung cancer occur each year.[1] In Canada, approximately 26 000 people are diagnosed with lung cancer and 20 500 die of it each year.[2] There are two primary histologic types, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). SCLC accounts for 10-15% of lung cancers and can only be reliably differentiated from NSCLC through a biopsy.[3] SCLC is, unfortunately, associated with high rates of metastasis and rapid mortality. It is believed that almost all patients have microscopic metastases, and at least 60% show radiographic evidence of metastases at diagnosis.[4]

Optimal treatment differs by stage. SCLC was originally broken up into two classifications; limited stage (LS) and extensive stage (ES). In LS-SCLC the malignancy is confined to the lung and regional lymph nodes, while ES-SCLC has spread outside a single radiation field.[3–5] Due to variation in prognosis within LS-SCLC, staging has been updated according to the Tumour, Node, Metastasis (TNM) classification.[5] This re-classification is important for predicting survival, but the evidence driving treatment decisions still rests primarily on the LS/ES classification. If left untreated, SCLC is usually fatal within less than four months.[6] This rapid progression makes treatment both important and time sensitive.

The primary treatment for LS-SCLC is the concurrent use of chemotherapy and radiation, while treatment of ES-SCLC is built on chemotherapy alone.[6,7] The combination of a platinum based agent and etoposide has been found to be the most effective regimen.[7,8] The major aim of these treatments is to relieve symptoms and prolong life. SCLC is very responsive to treatment, with objective response rates of 85-95% in LS-SCLC and 65–85% for ES-SCLC.[3,7] These responses often occur quickly, facilitating treatment of patients who would be too unwell to receive chemotherapy in many other solid organ malignancies.

Surgery is offered to less than 5% of individuals with “very limited stage disease” (small primary tumour with no lymph node involvement). [8–10]Recent studies have shown five-year survival rates ranging from 45-85% for those who undergo surgical resection followed by standard chemotherapy.[8,10] While advances have been made in treatment of many other solid tumours, including NSCLC, little has changed in systemic therapy for SCLC.[9,11] Recent research has started to unlock the SCLC genome. Numerous studies have attempted to take advantage of the pathways and mechanisms implicated, but have failed to show any clinical benefit.[11–13]

Performance status (PS) quantifies how disease affects patients’ daily function and has long been instrumental in treatment decisions as it is correlated with both quality of life and survival.[14] The Eastern Cooperative Oncology Group (ECOG) developed a PS score that is a robust prognostic factor for cancer patients and is used widely by medical oncologists as a cornerstone of treatment decisions.[14,15] In most malignancies, potential benefit with chemotherapy is believed to disappear in patients with ECOG PS 3-4 (poor PS), therefore, disease-specific guidelines avoid aggressive treatment. However, in SCLC, consensus opinion does suggest offering these patients chemotherapy due to high rates of rapid response.[7] Unfortunately, there is a lack of data and clear evidence to help justify this practice for patients with PS 3-4. This leads to uncertainty on treatment decisions and outcomes, which translates into challenges accurately counselling patients and highlights the need for further research on PS and other prognostic factors.[16]

In NSCLC, there is evidence to suggest that using cisplatin compared to carboplatin (both platinum agents) results in better response rates and superior survival.[17] This evidence has established cisplatin as the preferred agent in patients with adequate performance status and organ function despite its greater toxicity.

Specifically, cisplatin has higher rates of fatigue, nausea, vomiting, ototoxicity, nephrotoxicity, and thrombosis.[17] There has been comparatively little research on this question in SCLC. Existing studies suggest that carboplatin and cisplatin may provide equivalent benefits in SCLC patients, yet many medical oncologists still use cisplatin preferentially.[18]

This practice may be causing toxicity without an associated gain in response or survival. This concern is perhaps especially important for patients with poor PS who are less well and more vulnerable to adverse events. There has also been minimal research on this group of patients with poor PS. An understanding of factors influencing survival is essential for practicing oncologists to accomplish treatment planning, clinical trial design, and individual patient prognostic counseling.[19–21]

Individual studies have failed to include a full spectrum of possible prognostic factors, allowing an important possibility of confounding in their multivariable modeling. Many have also limited their cohorts to patients with good performance status, either because the patients come from clinical trials or through choice.[22] Exploring the differences in outcomes among patients diagnosed with SCLC in Manitoba and comparing response rates and survival by use of carboplatin or cisplatin will lead to improved planning around SCLC treatment.

Methods:

Cohort and Data Collection: We conducted a retrospective cohort study of Manitoba patients diagnosed with SCLC between January 1, 2004 and December 31, 2013. The Manitoba Cancer Registry (MCR) was used to define the cohort of patients diagnosed with SCLC, which was then limited to patients who were seen by a medical oncologist and/or received chemotherapy. A combination of the MCR, Manitoba Health physician billing data, Drug Program Information Network (DPIN), and Hospital Discharge Abstracts were used to acquire demographic, oncologic, treatment, and outcome data. The MCR is an administrative database that records information on all invasive neoplastic diagnoses in Manitoba (except non-melanoma skin cancer) and is 95-98% complete for cancer ascertainment.[23,24] Chart review was completed to add data not included in administrative databases, such as performance status, smoking status, blood work, chemotherapy regimen used, number of cycles, and response to treatment.

Response rate was defined as the presence of a post treatment decrease in tumour burden as stated in physician notes or radiology reports. Response to 1st line treatment was categorized into; complete or partial, stable, progression or unknown. Complete or partial response was noted when tumour burden either completely resolved or decreased in size. Stable disease was noted when tumour size remained constant and progression was defined as any increase in tumour burden or new metastases. Progression-free survival was defined as the time from first treatment until first radiographic progression or death. Overall survival, the primary outcome, was defined as the period of time from first treatment until death or censoring. Performance status was categorized using ECOG PS [Appendix]. PS categories were defined as good (ECOG PS 0), adequate (ECOG PS 1-2) and poor (ECOG PS 3- 4).

Treatment toxicity and compliance data was recorded and used to compare cisplatin and carboplatin. Hematological toxicities included neutropenia - defined as an absolute neutrophil count (ANC) <1.5, thrombocytopenia - a platelet count <100 and febrile neutropenia - ANC <1.5 and a documented fever over 38°C. Venous thrombosis was recorded when there was a reported DVT/PE and arterial thrombosis was recorded when there was a reported MI/CVA/arterial clot. Non-hematological toxicities include nephrotoxicity - defined as a creatinine increase of >49, neurotoxicity - defined as patient reported neuropathy and fatigue - defined ad a patient reported significant increase in fatigue. Nausea and vomiting was recorded if patients

reported any instances post treatment and ototoxicity was defined as any patient reporting hearing loss or tinnitus. Transfusion data was also collected if the patient required any infusion of packed red blood cells, platelets or fresh frozen plasma.

Compliance variables included the presence of a 1st line dose reduction, which was any change from standard dosing regimen at the start of treatment or during the treatment course. Course delays were also noted to be any delay of more than 4 days from projected cycle start date. A chemotherapy switch during 1st line treatment was defined as any change in platinum agent. Switch reason was also documented as either due to toxicity, unknown or other. The final measure of treatment compliance was whether or not the patient received the projected course of at least four cycles of chemotherapy.

Analysis: Demographic and cancer variables were evaluated descriptively – mean and standard deviation or median and range for continuous variables and proportions for categorical variables. We will then proceed with a comparative analysis of outcomes by treatment received. Response rates were compared using the Pearson Chi-squared test. Progression-free survival and overall survival were calculated using the methods of Kaplan and Meier, with between group testing using the logrank test.

We then proceeded with univariable analysis of the effect of each variable on survival using the Cox proportional hazard (PH) regression method. Variables with a p-value of ≤0.1 were included in the multivariable modeling process. Multivariable analysis was conducted in order to determine which prognostic factors were independently associated with overall survival. As the variable of interest, treatment with cisplatin or carboplatin was included regardless of p-value in the initial model, but otherwise covariates were included or excluded using the purposeful selection of covariates method. To ensure the accuracy of our model we split cisplatin and carboplatin patients into two groups; completers and incompleters. Patients were included into the 'completers' group if they completed 4 treatment cycles (normal regimen is 4-6 cycles). The splitting of the groups ensured that the assumptions of the PH model were not violated and the treatment effect could be accurately quantified.

Ethics approval was received from the University of Manitoba Research Ethics Board.

Results

Patient Characteristics

Table 1 summarizes the demographics of the 531 patients diagnosed with SCLC and in Manitoba between January 1, 2004 and December 31, 2013 and who were treated with chemotherapy. Of those, 392 (73.8%) received cisplatin and 139 (26.2%) received Carboplatin as their first line platinum agent. The median age of those who received cisplatin was 64 (range 35-87), compared to a median age of 70 (range 44-85) for those treated with carboplatin ($p<0.0001$). A larger proportion of patients treated with carboplatin had ES – 69.8% versus 54.8% of patients treated with cisplatin ($p<0.001$). At the onset of treatment with cisplatin, 18.9% of the patients had an ECOG PS of 0, 72.2% had a PS of 1-2, 7.4% had a PS of 3-4 and 1.0% had an unknown PS. While, 7.2% of patients treated with carboplatin had a PS of 0, 78.4% had a PS of 1-2, 13.7% a PS of 3-4 and 1.0% had an unknown PS ($p<0.001$). Both treatment groups were very similar in regards to smoking history. Elevated LDH (>230) was more often seen in cisplatin patients ($p<0.01$). Abnormal serum sodium, and low hemoglobin, known prognostic factor for SCLC were not significantly different between the two groups.

Treatment Received
Overall, 75.7% of patients received thoracic RT, although there were significant differences between the two groups (Table 2) - 80.4% of the cisplatin group versus 62.6% of the carboplatin group (p<0.0001). Concurrent RT was delivered to 13.3% of the cisplatin group, but only 6.5% of those who received carboplatin. Cisplatin patients received consolidative RT in 19.9% of cases compared to 10.8% of carboplatin patients (p<0.01). Prophylactic Cranial Irradiation (PCI) was given to 24.2% of those treated with cisplatin compared to 14.4% of the carboplatin group (p<0.05). More carboplatin patients received their 1st chemotherapy as an inpatient compared to cisplatin patients (p<0.01). Surgical resection was undertaken in 5.4% of cisplatin patients and only 3.6% of carboplatin patients (p=0.4).

Response
Treatment responses are summarized in Table 3. Patients who received cisplatin had complete or partial response in 69.1% of cases and had stable disease in 6.1%. Those who received carboplatin as first line chemotherapy had a complete or partial response in 58.3% of cases, and had stable disease in another 5.0%. The number of patients who progressed on 1st line chemotherapy was 9.2% and 10.8% for cisplatin and carboplatin respectively. Unknown response was recorded for 15.3% of cisplatin patients and 25.9% of carboplatin patients. Response rates were not significantly different (p=0.59). Survival rates at 1, 2, and 5 years were superior in patients treated with cisplatin versus carboplatin, as well as in LS compared to ES disease (Table 3). Median overall survival was also longer in patients receiving cisplatin (332 days v 245 days p<0.0005) (Figure 1A). Median progression-free survival was significantly longer with cisplatin versus carboplatin (219 days v 198 days p<0.01) treatment groups (Figure 1B).

Univariate Cox regression was completed to compare cisplatin completers to carboplatin completers, carboplatin incompleters and cisplatin incompleters on OS and PFS (figures 1,3). When compared to cisplatin completers on OS, the carboplatin completers had a hazard ratio (HR) of death of 1.27, this showed statistical significance at p<0.05. The Carboplatin incompleters had a ratio of 2.63 (p<0.01) and the cisplatin incompleters a ratio of 1.36 (p<0.06). PFS showed similar differences between the groups but a significant difference was only seen in carboplatin incompleters, with a HR of 1.91(p<0.01). Carboplatin incompleters had a HR of 1.23 which showed a trend towards significance (p=0.09).

A multivariable Cox PH regression was built to look at OS and PFS, which included treatment, PS, stage, gender, age at diagnosis, LDH, Na, Hb, Lung RT, PCI and setting as covariates (Table 4). The model showed that, when adjusting for covariates, cisplatin and carboplatin completers had almost identical HRs (1.00 v 1.01), while only Carboplatin incompleters were trending towards significance with a HR of 1.47 (p=0.08). ECOG PS, tumour stage and being female also had statistically significant positive associations with OS. Abnormal LDH and Na+ were also had a significant negative impact on OS. The analysis for PFS showed that cisplatin and carboplatin completers had nearly identical HRs (1.00 v 0.95). While stage and elevated LDH were seen to be negative prognostic factors. Receiving PCI had a strong association with improved OS and PFS. Increased age at diagnosis had no significant impact on either OS or PFS.

Toxicities
Toxicity profiles are outlined in Table 5. Hematologic toxicities included neutropenia (74.7% vs. 57.6%, p<0.0001), thrombocytopenia (27.6% vs. 35.3%, p=0.1), venous thrombosis (6.6% vs. 2.9%, p=0.1) and arterial thrombosis (1.3% vs. 0.0%, p=0.3) in the cisplatin and carboplatin treatment groups respectively. Rates of transfusion of either packed RBC, platelets or fresh frozen plasma were similar between the two groups. Non-hematological toxicities that occurred in the cisplatin and carboplatin treatment groups, included nephrotoxicity (13.5% vs. 2.9%, p<0.0001), neurotoxicity (12.0% vs. 0.7%, p<0.0001), nausea or vomiting (42.6% vs. 28.1%, p<0.01), ototoxicity (1.0% vs. 0.0%, p=0.5) and fatigue (32.7% vs. 34.5%, p=0.7).

Compliance with treatment is summarized in Table 6. First line chemotherapy dose was reduced in 76.8% and 82.7% of cisplatin and carboplatin treatment regimens respectively (p=0.14). A delay in chemotherapy administration was seen in 78.6% of cisplatin and 67.6% of carboplatin patients (p<0.01). The platinum drug had to be changed in 9.2% of patients first treated with cisplatin compared to only 3.6% of those treated with carboplatin (p<0.05).

Discussion

This retrospective analysis of SCLC patients in Manitoba aimed to look at the effect of cisplatin versus carboplatin on patient outcomes. There has been relatively little research to back up current physician practice of favouring cisplatin as the first line platinum agent.[18] Previous research has indicated that carboplatin and cisplatin may show near equivalent efficacy, with carboplatin showing less toxicity.[17,25] When adjusted for confounding variables in the present study, cisplatin and carboplatin chemotherapy show equal efficacy in terms of OS and PFS when a standard regimen of at least 4 cycles is completed. The main difference found between the two platinum agents was their toxicity profiles, with cisplatin causing more frequent adverse events.

Due to the nature of this study being a retrospective cohort analysis, the groups were not balanced in terms of prognostic factors. These differences mirror current treatment practices, where healthier patients are commonly given cisplatin instead of carboplatin based on improved outcomes with cisplatin extrapolated from NSCLC trials.[17] Carboplatin is used as first line treatment due to its favourable toxicity profile for those who are very ill, are who have contraindications to cisplatin. It was important to use rigorous statistical methods to help control for potential confounders and get a less biased assessment of the differential effect of cisplatin and carboplatin. Comparing the two drugs on OS using a univariate Cox PH regression, patients receiving cisplatin had a significantly better OS than those treated with carboplatin. When the analysis was taken further with a multivariable Cox PH regression, which adjusts for many known prognostic factors, the cisplatin advantage all but disappears. The HRs for cisplatin and carboplatin completers are nearly identical, with only carboplatin incompleters having a significantly poorer HR. This model of analysing OS helps adjust for the imbalances in the groups initially and allows us to focus on the actual effect of the treatment. In our case it showed that as long as patients completed the standard regimen of chemotherapy, the two platinum agents had an equal effect on improving OS. For PFS, the multivariable Cox PH regression showed no significant differences between treatments. These findings are consistent with a different retrospective cohort analysis that found negligible differences in efficacy between cisplatin and carboplatin.[26] Due to lower observed toxicity with carboplatin and equivalent responses, in equivalently healthy patients, we would expect more patients treated with carboplatin to complete their course of treatment.

Our results show similarities to other studies conducted on SCLC. A retrospective review by Karam et al., found similar non-significant differences between cisplatin and carboplatin in terms of OS and locoregional control.[27] A randomized control trial (RCT) from 2007 that focused on elderly and poor risk patients also found no significant differences between the platinum agents in regards to response rate or OS.[28] Our study was more inclusive, as it assessed all patients who were diagnosed and treated for SCLC regardless of age or risk factors. A meta-analysis by Rossi et al. that reviewed four RCTs comparing cisplatin and carboplatin, similarly showed equivalent efficacy in OS and PFS.[25] This review did have some differences in eligibility criteria as the RCTs were limited by age, PS or stage. The equal efficacy found in SCLC differs from the literature on NSCLC where cisplatin shows superiority in outcomes compared to carboplatin.[29,30]

Cisplatin's worse toxicity profile relative to carboplatin's is well documented.[18,31] Our results confirmed this profile, despite carboplatin being the treatment choice for those with poorer PS. Cisplatin was shown to have significantly more neutropenia, nephrotoxicity, neurotoxicity, and treatment associated nausea/vomiting. These toxicities can have major implications on patients well-being during and after treatment. A study by Hatfield et al., showed that patients treated with carboplatin had fewer hospital admissions, ICU stays and ED visits compared to those receiving cisplatin.[32] Hospitalizations can have a profound effect on physical and psychosocial health.[32] Toxicities increase the risk of chemotherapy delay and potentially changes the number of planned cycles. These missed cycles and delays have been correlated with worse prognosis and increased mortality.[33] Chemotherapy induced toxicity also negatively impacts many facets of one's life including; physical functioning, self-care, physical activity, mobility and mood.[34] The added toxicity related to cisplatin can, therefore, have a major impact on further treatment as well as quality of life and should be avoided when treatments result in equivalent cancer control.

As one would expect, given the greater toxicity seen with cisplatin, patient treated with carboplatin in our study had some improvements in treatment compliance. While carboplatin doses were reduced slightly more often, delays in treatment were 10% more common in those receiving cisplatin, and almost 9% of cisplatin patients needed to switch their first line agent due to toxicity. These differences in compliance and toxicity outline the importance of choosing the right chemotherapy agent at the outset. Dose intensity has been proven to impact PFS and OS.[35] When given a substantially reduced dose, as seen with complications related to toxicity, there are increases in tumour progression and mortality.[35,36] Dose density refers to the amount of drug given per unit of time. Optimal dose density requires that delays in treatment be kept to a minimum. Delays in chemotherapy administration due to toxicity have been associated with decreased OS.[37] These findings further highlight the importance of minimizing therapeutic toxicities.

Understanding factors that influence survival is essential for treatment planning and individual patient prognostic counseling.[19] Prognostic counseling is important to both oncologists and patients as it helps with treatment benefit predictions and end of life planning. Several prognostic factors have been well defined for SCLC. These include stage, PS, sex, LDH, Na+, Hgb, continued smoking, certain metastatic sites and Cushing's syndrome.[3,38] Our study also examined some of these prognostic factors. Stage, sex, LDH, Na+ and Hgb were all found to have a significant prognostic impact on OS. These findings help cement the importance of these variables as prognostic factors and they should continue to be of importance in making treatment decisions and providing patient counselling.

RT can be an important aspect of SCLC treatment due to its impact on survival and the radiosensitizing effects of chemotherapy. These therapies work best for LS disease when given concurrently, but can also be effective if given as a consolidative treatment shortly after chemotherapy has finished.[39] It has been shown to improve PFS and OS and be an integral part of SCLC management.[39] In our study almost 76% of patients received some form of thoracic RT, while nearly 22% received PCI. Of those receiving cisplatin, 13% received concurrent RT, compared to only 6.5% of carboplatin patients. This again shows the difference in the health and stage of the groups at the onset of treatment. Similar discrepancies were found between the two groups in receipt of PCI. These differences between the two treatment groups add to perceived OS and PFS benefit of cisplatin. Our study demonstrates similar results to those seen in previous RCTs, in that thoracic RT and PCI have a benefit on OS and PFS.[3,39]

The main limitation of this study is that it is a retrospective cohort study and therefore at greater risk of confounding than a randomized controlled trial. There were biases in patient treatment selection and hence inherent differences between the two groups at the onset of treatment. The use of rigorous statistical methods/modeling to control for confounding factors was employed, but additional confounding may still remain. As this was a chart review based study, we were only able to collect variables already recorded and

accurate recordkeeping is assumed. Despite these limitations, our study helps demonstrate the real-world practice pattern of medical oncologists regarding the prescription of cisplatin and carboplatin and confirms the equivalence of the two treatments demonstrated in RCTs.

In conclusion, our study helps demonstrate that cisplatin and carboplatin are both effective in treating patients with SCLC. No statistically significant differences were found between the two treatments in terms of OS and PFS, when a complete course of treatment was given. Carboplatin caused less toxicity and increased treatment compliance. This equal efficacy and improved toxicity profile makes carboplatin an attractive 1st line treatment alternative to cisplatin. The existing research has also shown equivalent efficacy and a favorable toxicity profile for carboplatin, yet treatment practices have not been altered. Changes need to be implemented to improve knowledge translation to practicing oncologists. It is important that oncologists take into account quantity and quality of life when making treatment decisions for individuals with SCLC.

References:

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90. doi:10.3322/caac.20107.
2. Statistics CCSsACoC. Canadian Cancer Statistics 2013. 2013.
3. Devita V, Lawrence T, Rosenberg S. *DeVta, Hellman, and Rosenberg's Cancer Principles & Practice of Oncology*. 9th ed. Philadelphia: Wolters Kluwer Health; 2011.
4. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol*. 2006;24(28):4539-4544. doi:10.1200/JCO.2005.04.4859.
5. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol*. 2007;2(12):1067-1077. doi:10.1097/JTO.0b013e31815bdc0d.
6. Pelayo Alvarez M, Westeel V, Cortes-Jofre M, Bonfill Cosp X. Chemotherapy versus best supportive care for extensive small cell lung cancer. *Cochrane database Syst Rev*. 2013;(11):CD001990. doi:10.1002/14651858.CD001990.pub3.
7. Kalemkerian GP, Akerley W, Bogner P, et al. Small cell lung cancer. *J Natl Compr Canc Netw*. 2013;11(1):78-98.
8. Dowell JE. Small cell lung cancer: are we making progress? *Am J Med Sci*. 2010;339(1):68-76. doi:10.1097/MAJ.0b013e3181bccef5.
9. Potter DS, Galvin M, Brown S, et al. Inhibition of PI3K/BMX Cell Survival Pathway Sensitizes to BH3 Mimetics in SCLC. *Mol Cancer Ther*. 2016;15(6):1248-1260. doi:10.1158/1535-7163.MCT-15-0885.
10. de Hoyos A, DeCamp MM. Surgery for small cell lung cancer. *Thorac Surg Clin*. 2014;24(4):399-409. doi:10.1016/j.thorsurg.2014.07.005.
11. Sharp A, Bhosle J, Abdelraouf F, Popat S, O'Brien M, Yap TA. Development of molecularly targeted agents and immunotherapies in small cell lung cancer. *Eur J Cancer*. 2016;60:26-39. doi:10.1016/j.ejca.2016.03.004.
12. Belani CP, Dahlberg SE, Rudin CM, et al. Vismodegib or cixutumumab in combination with standard chemotherapy for patients with extensive-stage small cell lung cancer: A trial of the ECOG-ACRIN Cancer Research Group (E1508). *Cancer*. 2016. doi:10.1002/cncr.30062.
13. Han J-Y, Kim HY, Lim KY, Hwangbo B, Lee JS. A phase II study of nintedanib in patients with relapsed small cell lung cancer. *Lung Cancer*. 2016;96:108-112. doi:10.1016/j.lungcan.2016.04.002.
14. Orr ST, Aisner J. Performance status assessment among oncology patients: a review. *Cancer Treat Rep*. 1986;70(12):1423-1429.
15. Salloum RG, Smith TJ, Jensen GA, Lafata JE. Using claims-based measures to predict performance status score in patients with lung cancer. *Cancer*. 2011;117(5):1038-1048. doi:10.1002/cncr.25677.
16. Baldotto CS, Cronemberger EH, De Biasi P, et al. Palliative care in poor-performance status small cell lung cancer patients: Is there a mandatory role for chemotherapy? *Support Care Cancer*. 2012;20(11):2721-2727. doi:10.1007/s00520-012-1392-0.
17. de Castria TB, da Silva EMK, Gois AFT, Riera R. Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer. *Cochrane database Syst Rev*. 2013;8(8):CD009256. doi:10.1002/14651858.CD009256.pub2.
18. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: The COCIS meta-analysis of individual patient data. *J Clin Oncol*. 2012;30(14):1692-1698. doi:10.1200/JCO.2011.40.4905.
19. Buccheri G, Ferrigno D. Prognostic factors of small cell lung cancer. *Hematol Oncol Clin North Am*. 2004;18(2):445-460. doi:10.1016/j.hoc.2003.12.011.

20. Cerny T, Blair V, Anderson H, Bramwell V, Thatcher N. Pretreatment prognostic factors and scoring system in 407 small-cell lung cancer patients. *Int J cancer*. 1987;39(2):146-149.
21. Souhami RL, Bradbury I, Geddes DM, Spiro SG, Harper PG, Tobias JS. Prognostic significance of laboratory parameters measured at diagnosis in small cell carcinoma of the lung. *Cancer Res*. 1985;45(6):2878-2882.
22. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. *J Clin Oncol*. 1990;8(9):1563-1574.
23. Roos LL, Mustard CA, Nicol JP, et al. Registries and administrative data: organization and accuracy. *Med Care*. 1993;31(3):201-212.
24. Robinson JR, Young TK, Roos LL, Gelskey DE. Estimating the burden of disease. Comparing administrative data and self-reports. *Med Care*. 1997;35(9):932-947.
25. Rossi A, Martelli O, Di Maio M. Treatment of patients with small-cell lung cancer: From meta-analyses to clinical practice. *Cancer Treat Rev*. 2013;39(5):498-506. doi:10.1016/j.ctrv.2012.09.006.
26. Santana-Davila R, Szabo A, Arce-Lara C, Williams CD, Kelley MJ, Whittle J. Cisplatin versus carboplatin-based regimens for the treatment of patients with metastatic lung cancer. an analysis of Veterans Health Administration data. *J Thorac Oncol*. 2014;9(5):702-709. doi:10.1097/JTO.0000000000000146.
27. Karam I, Jiang SY, Khaira M, Lee CW, Schellenberg D. Outcomes of small cell lung cancer patients treated with cisplatin-etoposide versus carboplatin-etoposide. *Am J Clin Oncol*. 2015;38(1):51-54. doi:10.1097/COC.0b013e31828aab2a.
28. Okamoto H, Watanabe K, Kunikane H, et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. *Br J Cancer*. 2007;97(2):162-169. doi:10.1038/sj.bjc.6603810.
29. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst*. 2007;99(11):847-857. doi:10.1093/jnci/djk196.
30. Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Meta-analysis of randomized clinical trials comparing Cisplatin to Carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2004;22(19):3852-3859. doi:10.1200/JCO.2004.02.109.
31. Caprario LC, Kent DM, Strauss GM. Effects of chemotherapy on survival of elderly patients with small-cell lung cancer: analysis of the SEER-medicare database. *J Thorac Oncol*. 2013;8(10):1272-1281. doi:10.1097/JTO.0b013e3182a007ba [doi]\r01243894-201310000-00008 [pii].
32. Hatfield LA, Huskamp HA, Lamont EB. Survival and Toxicity After Cisplatin Plus Etoposide Versus Carboplatin Plus Etoposide for Extensive-Stage Small-Cell Lung Cancer in Elderly Patients. *J Oncol Pract*. 2016;12(7):666-673. doi:10.1200/JOP.2016.012492.
33. Deek MP, Kim S, Ahmed I, et al. Prognostic Impact of Missed Chemotherapy Doses During Chemoradiation Therapy for Non-Small Cell Lung Cancer. *Am J Clin Oncol*. 2016. doi:10.1097/COC.0000000000000293.
34. Fiteni F, Anota A, Bonnetain F, et al. Health-related quality of life in elderly patients with advanced non-small cell lung cancer comparing carboplatin and weekly paclitaxel doublet chemotherapy with monotherapy. *Eur Respir J*. 2016. doi:10.1183/13993003.01695-2015.
35. Wood WC, Budman DR, Korzun AH, et al. Dose and Dose Intensity of Adjuvant Chemotherapy for Stage II, Node-Positive Breast Carcinoma. *N Engl J Med*. 1994;330(18):1253-1259. doi:10.1056/NEJM199405053301801.
36. Budman DR, Berry DA, Cirrincione CT, et al. Dose and Dose Intensity as Determinants of Outcome in the Adjuvant Treatment of Breast Cancer. *J Natl Cancer Inst* . 1998;90(16):1205-1211. doi:10.1093/jnci/90.16.1205 .
37. Liutkauskiene S, Janciauskiene R, Jureniene K, Grizas S, Malonyte R, Juozaityte E. Retrospective

analysis of the impact of platinum dose reduction and chemotherapy delays on the outcomes of stage III ovarian cancer patients. *BMC Cancer*. 2015;15:105. doi:10.1186/s12885-015-1104-5.

38. Chen Y, Yu H, Wu C, et al. Prognostic value of plasma D-dimer levels in patients with small-cell lung cancer. *Biomed Pharmacother*. 2016;81:210-217. doi:10.1016/j.biopha.2016.02.030.
39. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet*. 2015;385(9962):36-42. doi:10.1016/S0140-6736(14)61085-0.

Tables:

Table 1: Patient Demographics

Characteristic	Overall Patients n =	%	Cisplatin n =	%	Carboplatin n =	%	Statistical test	p-value
Population	531		392	73.8	139	26.2		
Age, years							t-test	<.0001
Median	66		64		70			
Range	52.0 (low 35; high 87)		52 (low 35; high 87)		41 (low 44; high 85)			
Sex							chi-square	0.055
Male	252	47.5	196	50.0	56	40.3		
Female	279	52.5	196	50.0	83	59.7		
ECOG PS							chi-square	0.001
0	84	15.8	74	18.9	10	7.2		
1 - 2	392	73.8	283	72.2	109	78.4		
3 - 4	48	9.0	29	7.4	19	13.7		
Unknown	5	0.9	4	1.0	1	0.7		
Stage							chi-square	0.0009
LS	217	40.9	177	45.2	40	28.8		
ES	309	58.2	212	54.1	97	69.8		
Unknown	5	0.9	3	0.8	2	1.4		
TNM stage				0.0			chi-square	0.1327
I	20	3.8	16	4.1	4	2.9		
II	23	4.3	19	4.8	4	2.9		
III	190	35.8	149	38.0	41	29.5		
IV	290	54.6	203	51.8	87	62.6		
Smoking Status							fisher's exact	0.678
Never smoked	8	1.5	5	1.3	3	2.2		
Ex-smoker	291	54.8	211	53.8	80	57.6		
Current Smoker	185	34.8	137	34.9	48	34.5		
Unknown	47	8.9	39	9.9	8	5.8		
Smoking Pack Years	450	84.7	334	85.2	116	83.5	t-test	0.1844
Median	40		40	10.2	40	28.8		
Range	225 (low 0; high 225)		116 (low 0; high 116)		225 (low 0; high 225)			
Elevated LDH							chi-square	0.0058
Yes	247	46.5	166	42.3	81	58.3		
No	236	44.4	185	47.2	56	40.3		
Unknown	40		34	8.7	1	0.7		
Abnormal Serum Na+							chi-square	0.7498
Yes	388	73.1	285	72.7	103	74.1		
No	143	26.9	107	27.3	36	25.9		
Unknown	0		0		0			
Low Hb							chi-square	0.7453
Yes	280	52.7	208	53.1	72	51.8		
No	241	45.4	176	44.9	65	46.8		
Unknown	10	1.9	8	2.0	2	1.4		

Abbreviations: ECOG - Eastern Cooperative Oncology Group LS - Limited Stage, ES - Extensive Stage, SES - socioceconomic status, Elevated LDH - >230, Abnormal Serum Na+ - <13 >147, Low Hb - M: <140, F: <120

Table 2: Treatment Received

Characteristic	Overall Patients n =	%	Cisplatin n =	%	Carboplatin n =	%	Statistical	p-
Thoracic RT Received							chi-square	<.0001
Yes	402	75.7	315	80.4	87	62.6		
No	130	24.5	78	19.9	52	37.4		
Thoracic RT Delivery							chi-square	0.002
None	220	41.4	146	37.2	74	53.2		
Concurrent	61	11.5	52	13.3	9	6.5		
Consolidative	93	17.5	78	19.9	15	10.8		
Palliative	156	29.4	115	29.3	41	29.5		
PCI Received							chi-square	0.016
Yes	115	21.7	95	24.2	20	14.4		
No	416	78.3	297	75.8	119	85.6		
1st Chemotherapy Setting							chi-square	0.002
Inpatient	83	15.6	50	12.8	33	23.7		
Outpatient	448	84.4	342	87.2	106	76.3		
Surgical Resection							chi-square	0.409
Yes	26	4.9	21	5.4	5	3.6		
No	505	95.1	371	94.6	134	96.4		

Abbreviations: RT - Radiotherapy , PCI - prophylactic cranial irradiation

Table 3: Response Variables

Characteristic	Overall Patients n =	Overall Patients %	Cisplatin n =	Cisplatin %	Carboplatin n =	Carboplatin %	Statistical	p-
Response to 1st Line								
Complete or Partial	352	66.3	271	69.1	81	58.3	chi-square	0.597
Stable	31	5.8	24	6.1	7	5.0		
Progression	51	9.6	36	9.2	15	10.8		
Unknown	96	18.1	60	15.3	36	25.9		
1 Year Survival Rate							chi-square	0.046
LS	135	25.4	115	29.3	20	14.4		
ES	77	14.5	57	14.5	20	14.4		
Combined	212	39.9	172	43.9	40	28.8		
2 Year Survival							Fisher's exact	0.306
LS	70	13.2	62	15.8	8	5.8		
ES	24	4.5	19	4.8	5	3.6		
Combined	94	17.7	81	20.7	13	9.4		
5 year survival							Fisher's exact	1
LS	22	4.1	19	4.8	3	2.2		
ES	6	1.1	6	1.5	0	0.0		
Combined	28	5.3	25	6.4	3	2.2		

Abbreviations: LS - Limited stage disaese; ES - Extensive stage disease

Table 4 Multivariable Cox PH Regression for Overall Survival & Progression Free Survival

Variable	Description	Overall Survival Hazard Ratio	Overall Survival p-value	Progression Free Survival Hazard Ratio	Progression Free Survival p-value
Treatment	Cisplatin Completers	REFERENCE	0.32	REFERENCE	0.29
	Carboplatin Completers	1.01 (0.78-1.31)		0.95 (0.73-1.22)	
	Carboplatin Incompleters	1.47 (0.96-2.24)		1.01 (0.64-1.59)	
	Cisplatin Incompleters	1.05 (0.72-1.52)		0.73 (0.51-1.06)	
ECOG PS	ECOG 0	REFERENCE	<0.01	REFERENCE	0.06
	ECOG 1-2	1.46 (1.09-1.89)		1.34 (1.02-1.77)	
	ECOG 3-4	1.96 (1.29-2.99)		1.58 (1.04-2.40)	
Stage	LS	REFERENCE	<0.05	REFERENCE	<0.01
	ES	1.38 (1.08-1.76)		1.59 (1.24-2.04)	
Sex	Male	REFERENCE	<0.05	REFERENCE	0.25
	Female	0.78 (0.64-0.96)		0.89 (0.73-1.08)	
LDH	Normal LDH	REFERENCE	<.0.0001	REFERENCE	<0.01
	Elevated LDH	1.55 (1.26-1.90)		1.38 (1.12-1.70)	
Na+	Normal Na+	REFERENCE	<0.01	REFERENCE	0.22
	Abnormal Na+	1.39 (1.12-1.74)		1.15 (0.92-1.43)	
Hgb	Normal Hgb	REFERENCE	0.96	REFERENCE	0.31
	Low Hgb	0.99 (0.81-1.22)		1.11 (0.91-1.35)	
Lung RT	No Lung RT	REFERENCE	0.08	REFERENCE	0.09
	Concurrent RT	0.69 (0.47-1.01)		0.74 (0.51-1.07)	
	Consolidative RT	0.70 (0.52-0.94)		0.75 (0.56-1.01)	
	Palliative	0.88 (0.70-1.10)		1.06 (0.84-1.33)	
Cranial RT	PCI	REFERENCE	<0.0001	REFERENCE	<0.0001
	No PCI	2.50 (1.91-3.28)		2.68 (2.05-3.50)	

Abbreviations: LS - Limited stage; ES - Extensive stage; LDH - Lactatedehydrogenase; Hgb - Hemoglobin; RT - Radiotherapy; PCI - Prophylactic cranial irradiation

Table 5: Toxicities

Characteristic	Overall Patients n =	Overall Patients %	Cisplatin n =	Cisplatin %	Carboplatin n =	Carboplatin %	Statistical Test	p-value
Neutropenia	373	70.2	293	74.7	80	57.6	Chi-square	<.0001
Thrombocytopenia	157	29.6	108	27.6	49	35.3	Chi-square	0.116
Febrile Neutropenia	40	7.5	34	8.7	6	4.3	Chi-square	0.087
Nephrotoxicity	57	10.7	53	13.5	4	2.9	Fisher's Exact	<.0001
Neurotoxicity	48	9.0	47	12.0	1	0.7	Fisher's Exact	<.0001
Received Transfusion	121	22.8	88	22.4	33	23.7	Chi-square	0.799
Nasuea or Vomitting	206	38.8	167	42.6	39	28.1	Chi-square	0.002
Ototoxicity	4	0.8	4	1.0	0	0.0	Fisher's Exact	0.577
Venous Thrombosis	30	5.6	26	6.6	4	2.9	Fisher's Exact	0.133
Arterial Thrombosis	5	0.9	5	1.3	0	0.0	Fisher's Exact	0.332
Fatigue	176	33.1	128	32.7	48	34.5	Chi-square	0.741

Table 6: Compliance

Characteristic	Overall Patients n =	Overall Patients %	Cisplatin n =	Cisplatin %	Carboplatin n =	Carboplatin %	Statistical Test	p-value
1st Line Chemotherapy Dose Reduced							Chi-square	0.1435
Yes	416	78.3	301	76.8	115	82.7		
No	115	21.7	91	23.2	24	17.3		
Course Delayed							Chi-square	0.0097
Yes	402	75.7	308	78.6	94	67.6		
No	129	24.3	84	21.4	45	32.4		
Switch During 1st Line							Fisher's Exact	0.0405
Yes	490	92.5	36	9.2	5	3.6		
No	41	7.7	356	90.8	134	96.4		
Switch Reason							Fisher's Exact	0.0036
Toxicity	37	7.0	35	8.9	2	1.4		
Unknown	3	0.6	1	0.3	2	1.4		
Other	1	0.2	0	0.0	1	0.7		
Received Projected Course							Chi-square	0.004
Yes	413	77.8	317	80.9	96	69.1		
No	118	22.2	75	19.1	43	30.9		

Figure 1A:

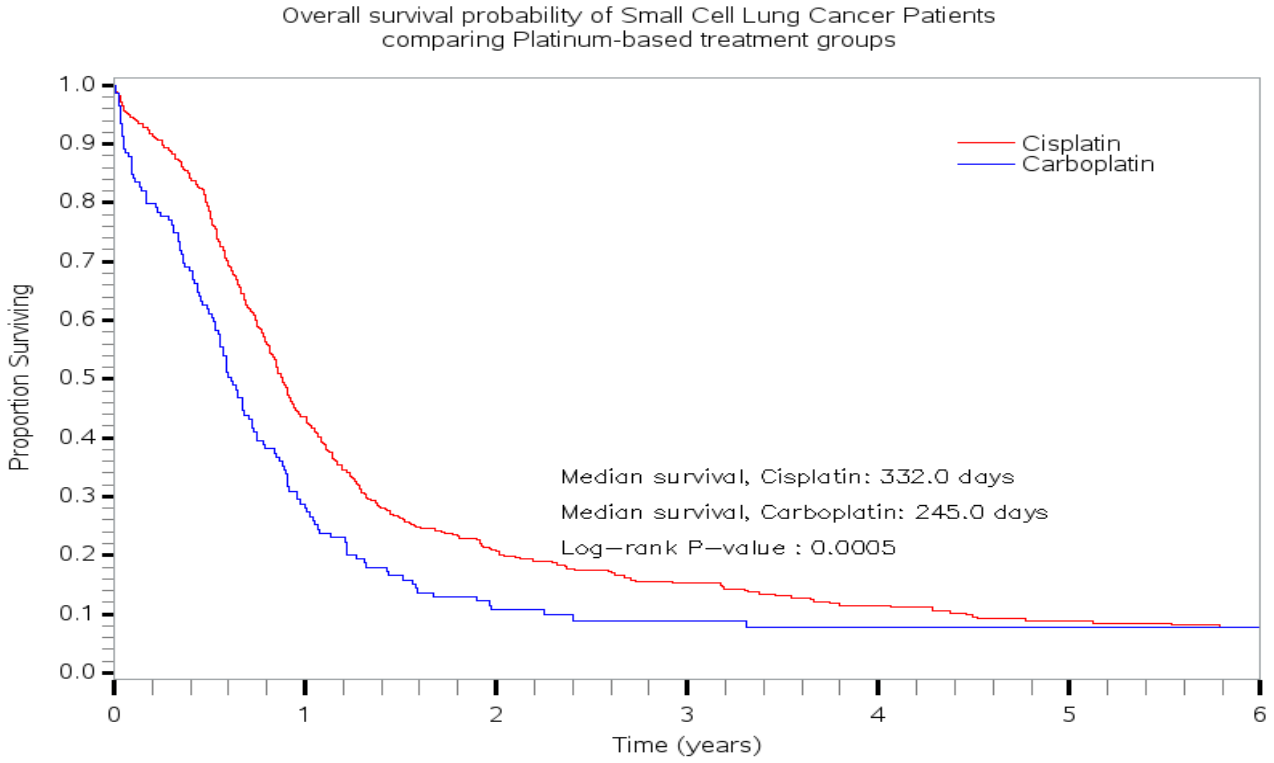
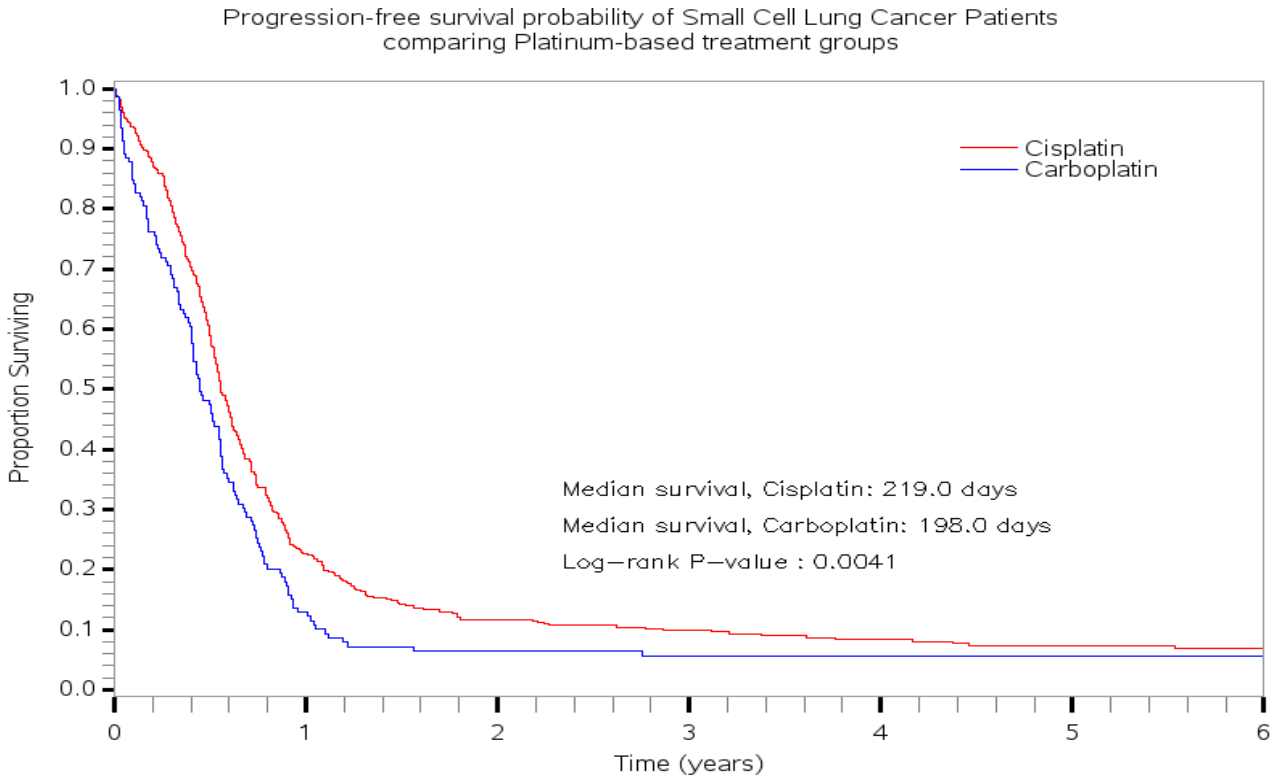


Figure 1B:



Appendix

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

From ECOG website - http://www.ecog.org/general/perf_stat.html