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Chapter 5

Treatment adherence in concurrent chemoradiation in patients with locally advanced non-small cell lung carcinoma: results of daily intravenous prehydration

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Abstract

Purpose: To test the hypothesis that daily intravenous pre-hydration decreases renal toxicity and improves chemotherapy adherence in patients receiving daily cisplatin to concurrent radiotherapy for locally advanced non-small cell lung cancer (NSCLC).

Patients and methods: Patients with locally advanced NSCLC were treated between 2008 and August 2012 with daily 6 mg/m² cisplatin as a bolus injection in 10 ml of saline and 66Gy/24fr radiotherapy in 32 days. Since January 2011, the administration of cisplatin was routinely preceded by intravenously pre-hydration with 1 Liter of natriumchloride 0.9%. Patients were divided in a pre-hydrated (PH) and non-pre-hydrated (NPH) cohort. Serum-creatinine and glomerular filtration rate (GFR) were assessed twice weekly during treatment. Retrospectively, baseline data, toxicity, treatment adherence and efficacy data were compared.

Results: Of the 356 patients 232 NPH patients and 100 PH patients were eligible. Patient-and treatment characteristics compared equally. The median of the maximum decrease in GFR was 24% and 8% for NPH and PH ($p < 0.01$), respectively. Sixty-nine percent of the patients in the NPH group completed the 24 administrations of cisplatin, as compared to 83% of the PH group ($p < 0.01$). Nineteen percent versus 2% of the patients in the NPH and PH group discontinued cisplatin treatment because of renal toxicity. Surprisingly, the incidence of acute esophageal toxicity grade ≥ 2 decreased following prehydration: 62% versus 34% ($p < 0.001$) for the NPH and PH group, respectively. The one-year survival was comparable between groups (75% for NPH and 71% for PH).

Conclusions: Daily pre-hydration was associated with a reduced rate of both renal and acute esophageal toxicity and an increased chemotherapy adherence in patients receiving daily dose cisplatin and concurrent radiotherapy for locally advanced NSCLC.

Introduction

Concurrent chemoradiation (CCRT) is the treatment of choice for locally advanced non-small cell lung cancer (NSCLC). The increase in survival for concurrent versus sequential chemo radiotherapy (+ 5.7 % at 3 years) or radiotherapy alone (+ 7% at 3 years) is mainly due to an improvement in local control of the disease (1). Several radiosensitizing agents are in use (2) and daily low dose cisplatin CCRT has shown to be an effective treatment regimen (3;4). Because of a milder toxicity profile, more patients are able to benefit from this treatment compared to regimen using high dose chemotherapy (5-7). It is believed that the completion of CCRT allows daily interaction between both modalities and optimizes the beneficial sensitizing effect (8;9).

Renal toxicity is the main cause of discontinuation of chemotherapy. In the case of upcoming renal toxicity, increase of fluid intake can be used to reduce toxicity and prevent chemotherapy discontinuation. Before 2011, we used a significant increase in serum creatinine (SC) during treatment as the reason to start pre-hydration (PH) before every administration of cisplatin. Despite this measure, approximately 20% of patients were not able to finish the chemotherapy because of renal toxicity (7). In an attempt to increase the tolerability, since January 2011, we introduced standard administration of PH before the cisplatin bolus injection for every patient treated with CCRT.

Published literature on PH describes the impact on toxicity and adherence of standard (30-80 mg/m²) or high dose (>100 mg/m²) cisplatin regimens (10-12). PH regimens vary from inpatient 24 hour pre-and post-hydration to outpatient protocols with only 2 hour of hyper hydration, irrespective of the cisplatin dosage. However, no data is available on the impact of PH combined with daily low dose cisplatin. Therefore, the aim of this study is to retrospectively compare PH to NPH in terms of treatment adherence, toxicity and survival.



Patients and Methods

Patient selection

From January 2008 until August 2012, a total of 356 patients with cytologically or histologically proven locally advanced NSCLC were treated with CCRT in our hospital. Patients were excluded from the current study if they did not receive the standard daily cisplatin, or were irradiated with dose per fraction exceeding 3 Gy, or were simultaneously treated for other primary tumors. Patient- and treatment characteristics were retrospectively collected, including WHO Performing Status (PS), age, gender, TNM according to the 7th edition for classification of lung cancer, number of cisplatin administrations and the causes of discontinuation, assessment of renal function and acute esophagus toxicity (AET).

Treatment

Cisplatin 6mg/m² was given as a 10 ml bolus injection, 1-2 hours prior to radiotherapy, for a total of 24 fractions over a period of 32 days. Some of the patients participated in a randomized clinical trial comparing survival with/without additional weekly cetuximab (<http://trialregister.nl>. Trial ID: NTR2230). The initial loading dose was 400 mg/m², followed by 250 mg/m² at a total of 6 administrations (13). The standard radiotherapy consisted of 24 fractions of 2.75 Gy, resulting in a total dose of 66 Gy to the primary tumor and involved lymph nodes. In case of large tumors or re-irradiation, where the mean lung dose exceeded 20 Gy, an alternative radiotherapy fractionation scheme was applied without changing the administration of cisplatin. All patients were treated with 7-field intensity modulated radiotherapy (IMRT). A 4D mid-ventilation planning CT scan with 5 mm slices was used (14). The gross tumor volume (GTV) encompassed the primary tumor and pathological lymph nodes on the planning CT-scan and 18-Fluorodeoxyglucose Positron Emission Tomography scan. The GTV was expanded to a planning target volume (PTV) using a margin of 12 mm + $\frac{1}{4}$ of the tumor peak-to-peak amplitude, the GTV lymph nodes with a uniform 12 mm margin. All treatment plans were optimized to have 99% of the PTV volume receiving at least 95% of the prescribed dose, with maxima of 115% allowed. Dose constraints and objectives were defined in biologically equivalent dose in 2 Gy per fraction EQD₂, converted voxel-by-voxel using linear-quadratic model: spinal cord dose ≤ 50 Gy ($\alpha/\beta=2$ Gy); esophagus volume

receiving 35 Gy (V_{35} Gy) $<65\%$ ($\alpha/\beta=10$ Gy), mean lung dose ≤ 20 Gy ($\alpha/\beta=3$ Gy), mean heart dose ≤ 40 Gy, 2/3 heart ≤ 50 Gy, and 1/3 heart ≤ 66 Gy ($\alpha/\beta=4$ Gy).

Laboratory parameters for renal function

Serum creatinine (SC) and glomerular filtration rate (GFR) were assessed at baseline and twice weekly during treatment (5 weeks). In case of a 20% increase of SC, the lab assay was measured daily. The accomplishment of chemotherapy was used as the primary endpoint for this study

Selection criteria

From January 2011, PH became standard of care for every NSCLC patient treated with CCRT. Chemotherapy was discontinued in case of a SC $\geq 30\%$ of baseline or when the GFR was reduced to < 60 ml/minute

From 2007 until January 2011, PH was only administered in case of a $\geq 20\%$ increase in SC during treatment. The same chemotherapy discontinuation criteria were used.

PH consisted of 1 L of sodium chloride (NaCl) 0.9% intravenously administered in one hour before the cisplatin bolus injection. In case of a history of cardiac failure or the occurrence of the syndrome of inappropriate anti-diuretic hormone secretion (SIADH), patients were given 500 ml of NaCl 0.9% while administering PH.

Acute esophagus toxicity

AET was prospectively scored by the treating physician or clinical nurse specialist at baseline, twice weekly during treatment and at week 1, 3, 7 and 12 after treatment using the Common Toxicity Criteria for adverse events (CTC AET) version 3.0. Acute and late esophagus toxicity is known to be RT dose related (15-18). To compare the esophageal RT dose between the NPH and PH patient groups, dose volume histograms (DVH) were compared. Treatment plans were first corrected for actual number of delivered RT fractions. Subsequently, the physical dose was converted voxel-by-voxel to EQD₂ using an α/β -ratio of 10 Gy. For evaluation, the published esophageal dosimetric predictors, such as the V35, V50 and equivalent uniform dose (EUD) with $n=0.13$ were compared (17).



Statistical analysis

The baseline characteristics, the prescribed radiotherapy dose, the number of cisplatin administration and the cause of cisplatin discontinuation were compared between PH and NPH patients, assuming no significant differences. The t-test, Wilcoxon rank sum test (for continuous variables), chi-squared test or Fisher's exact test (for categorical variable) were then applied to test this assumption. The effect size of the t-test, Wilcoxon rank sum test, chi-squared test and Fisher's exact test refers to Cohen's *d*, Hodges-Lehmann, Cramer's *V* value and odds ratio, respectively.

We then hypothesized that PH policy has an effect on renal function (SC and GFR) and therefore cisplatin adherence: SC and GFR were tested by Wilcoxon rank sum test and cisplatin adherence was tested by chi-squared test. The overall survival of the two groups was presented by Kaplan-Meier method and log-rank test was applied to test whether their survival curves were identical. Due to the multiple tests conducted simultaneously on this data set, we applied Bonferroni correction to reduce the chance of obtaining false positives (type I errors). The original critical p-value $\alpha=0.05$ was then adjusted to $\alpha=0.05/\text{number_of_tests}$. In the study we conducted 20 tests, leading to $\alpha=0.0025$. Thus, we obtain a significant result only if the p-value <0.0025 .

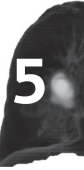
Results

Between January 2008 and August 2012, 356 consecutive patients were treated with CCRT for primary NSCLC. Excluded patients consisted of 12 patients receiving weekly instead of daily cisplatin because of a pilot study, 9 patients participating in a clinical trial with fraction doses exceeding 3 Gy per fraction, and 2 patients were treated simultaneously for head and neck cancer. Furthermore, only 1 patient was treated using 0.5L PH because of SIADH and this patient was also excluded. This resulted in a total of 332 eligible patients: 232 patients in the NPH group and 100 patients in the PH group. Patient baseline characteristics were comparable between the two groups (Table 1). The use of cetuximab was higher in the NPH group. The radiotherapy dose to GTV was significantly different between the two groups. Five patients (2%) in the NPH group and 3 patients (3%) in the PH group did not complete the intended RT schedule because of fever and/or refusal.

Table 1. Patient baseline characteristics and treatment between non pre-hydration (n=232) and pre-hydration (n=100) cohorts.

Characteristics	Non pre-hydration	Pre-hydration	Effect size*	P-value
median age (y) (range)	63 (32~87)	63 (38~83)	-0.076	0.54
Gender: (%) female	91 (39%)	42 (42%)	0.026	0.73
Performance status (%)				
WHO=0	74 (32%)	29 (29%)	0.029	0.69
1	151 (65%)	67 (67%)		
2	7 (3%)	4 (4%)		
TNM stage (%)			0.001	1.00
IA, IB	3 (1%)	2 (2%)		
IIA, IIB	18 (8%)	7 (7%)		
IIIA, IIIB	210 (91%)	89 (89%)		
4	1 (<1%)	2 (2%)		
Tumor stage (%)			0.102	0.33
0-1	37 (16%)	21 (21%)		
2	79 (34%)	26 (26%)		
3	48 (21%)	26 (26%)		
4	68 (29%)	27 (27%)		
N stage (%)			0.096	0.22
0	34 (15%)	16 (6%)		
1	19 (8%)	9 (9%)		
2	142 (61%)	52 (52%)		
3	37 (16%)	23 (23%)		
M stage (%)			2.340 (odds ratio)	0.59
0	230 (99%)	98 (98%)		
1	2 (1%)	2 (2%)		
Cetuximab (%)			0.116	<0.001
Yes	49 (21%)	3(3%)		
Prescribed RT dose to GTV (%)			20.327 (odds ratio)	<0.001
24x2.75Gy	229 (99%)	88 (88%)		
33x2Gy	1 (<1%)	4 (4%)		
30x2.25Gy	0 (0%)	4 (4%)		
30x2Gy	1 (<1%)	3 (3%)		
25x2Gy	1 (<1%)	1 (1%)		

* RT dose (standard RT vs. non-standard RT) and M stage were tested using Fisher's exact test, while other categorical variables were tested using chi-squared test.



Chemotherapy was completed by 160 patients (69%) in the NPH group and by 83 patients (83%) in the PH group ($p=0.01$) (Table 2). Although the p -value was not significant after the Bonferroni correction, we believe this finding was not likely by chance (false positive), because Bonferroni correction tends to be over-conservative and the observed odds ratio is reasonably large. The main reason for chemotherapy discontinuation was increased SC: grade 1-3 19% vs. 2% for the NPH and PH group, respectively ($p<0.001$) (Table 3).

Table 2. Number of cisplatin administrations in non pre-hydration ($n=232$) and pre-hydration ($n=100$) groups.

Variables	Non pre-hydration	Pre-hydration	Effect size*	P-value
Cisplatin (administrations)			2.192	0.01
<20	38 (16%)	13 (13%)		
20~23	34 (15%)	4 (4%)		
24	160 (69%)	83 (83%)		

*The proportion discontinued cisplatin (<24 vs. 24) was tested using Fisher's exact test.

Table 3. The cause and number of NSCLC patients treated with CCRT who discontinued cisplatin.

Variables	Non pre-hydration ($n=232$)	Pre-hydration ($n=100$)	Effect size*	P-value
Renal	44 (19%)	2 (2%)	0.088	<0.001
Refusal	4 (2%)	1 (1%)		
Nausea	10 (4%)	5 (5%)		
Cardiac	4 (2%)	1 (1%)		
Hematology	0 (0%)	1 (1%)		
Allergy	1 (<1%)	0 (0%)		
Other	8 (3%)	7 (7%)		
Unknown	1 (<1%)	0 (0%)		

* The proportion of renal toxicity (renal vs. non-renal) was tested using Fisher's exact test.

The maximum SC and the minimum GFR value during the treatment were used as the endpoint of the study. Both groups had comparable baseline SC and GFR values. In the NPH group, the increase in SC and the reduction in GFR were both significantly larger ($p<0.001$), indicating a higher impairment of renal function (Table 4 & 5).

In the NPH group a SC increase of $\geq 20\%$ was seen in 58% of the patients, and a SC increase of $\geq 30\%$ in 39%; for the PH group this was 21% and 9%, respectively ($p<0.001$).

A significant reduction in AET grade ≥ 2 was observed from 62% in the NPH group to 34% in the PH group ($p < 0.001$) (Table 6). On the other hand, the average esophageal dose tends to be lower in the PH group: V35Gy, V50Gy and EUD_{0.13} were 42.4% vs. 36.9% ($p = 0.01$, not significant after Bonferroni correction), 35.1% vs. 29.8% ($p = 0.02$) and 55.5 vs. 52.5 Gy ($p = 0.03$) for the NPH and the PH group, respectively.

Due to the discrepancy in dose distributions, we should adjust the dose difference when comparing AET between the two groups. Figure 1 plots the incidence of AET at fixed V50Gy bins for both groups, indicating that PH group yields a lower rate of AET, given the same dose. Additionally, we tested the observations in the PH group against a V50Gy prognostic model by Kwint et al. (26). They used a subset -133 patients - (57%) of the NPH group. In the test, we used a general statistic – the proportion of AET grade ≥ 2 – to test the proportion observed against the proportion predicted by the model. The null hypothesis was: the proportion of AET grade ≥ 2 predicted by the model (established from NPH group) is the same as the observed proportion of AET grade ≥ 2 . As a result, for NPH group, the observed proportion of AET grade ≥ 2 144/232 was not significantly different than the predicted value of 0.60 ($p = 0.46$). For PH group, the observed proportion of AET grade ≥ 2 34/100 was significantly lower than the model predicted value of 0.56 ($p < 0.001$). This result implies that the dose effect established from the NPH was no longer applicable to the PH group. In other words, PH was significantly associated with a lower rate of AET grade ≥ 2 , after adjusting for the RT dose effect.

Table 4. Serum creatinine: absolute value at baseline, maximum serum creatinine (as relative change to baseline), maximum increase over 20% or 30% for $n = 330$ NSCLC patients treated with CCRT. In both groups 1 patient is missing

Variables	non-preH n=231	PreH n=99	Effect size*	p-value
median Baseline (range)	72 (44~136)	71 (37~132)	1.000	0.551
median max_creat ($\Delta\%$) (range)	25.8 (-21.7~852.8)	7.6 (-18.7~51.0)	16.026	<0.001
Increase $\geq 20\%$	135 (58%)	21 (21%)	0.192	<0.001
Increase $\geq 30\%$	90 (39%)	9 (9%)	0.157	<0.001

Non-preH: non-prehydration; PreH: prehydration

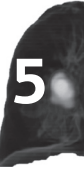


Table 5. Glomerular Filtration Rate (GFR): absolute value at baseline and minimum GFR during treatment weeks (as relative change to baseline) for n=256 patients.

Variables	non-preH n=156	PreH n=100	Effect size	p-value
Median baseline (range)	93 (46~155)	94 (46~163)	-1.000	0.795
Median min_GFR ($\Delta\%$) (range)	-24.0 (-97.0~32.3)	-8.4 (-37.7~26.8)	-14.500	<0.001

Table 6. Acute esophagus toxicity between non pre-hydration (n=232) and pre-hydration (n=100) cohorts.

Variables	Non pre-hydration	Pre-hydration	Effect size	P-value
CTCAE score			0.267	<0.001*
Grade 0-1	88 (38%)	66 (66%)		
Grade 2	88 (38%)	25 (25%)		
Grade 3	55 (24%)	9 (9%)		
Grade 4	1 (<1%)	0		

* Chi-squared test on 0-1 vs. 2-4; CTCAE= common toxicity criteria for adverse events

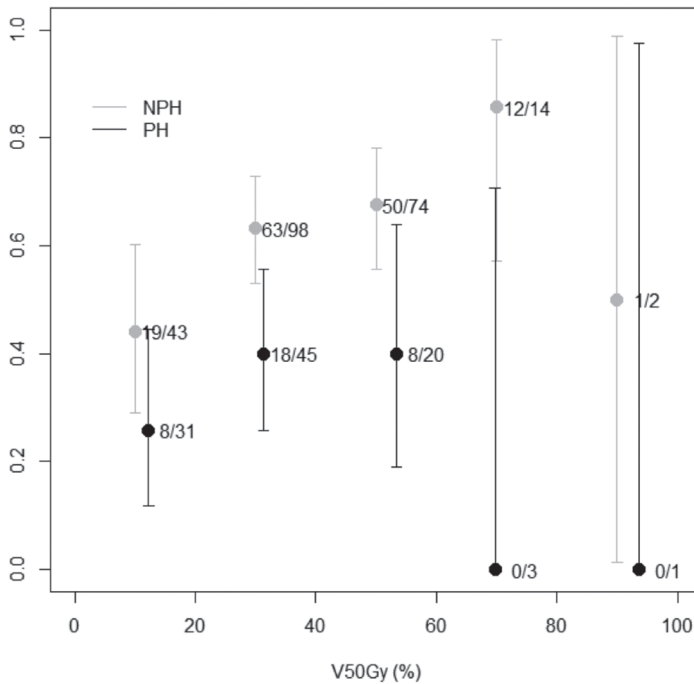


Figure 1: Incidence of acute esophagus toxicity grade ≥ 2 vs. V50Gy for NPH (n=232) and PH (n=100) groups. The incidence were plotted in fixed V50Gy bins: [0%-20%), [20%-40%), [40%-60%), [60%-80%) and [80%-100%). The Clopper-Pearson confidence interval was also plotted.

The median Follow up was 34.3 months (95% CI: 31.3-39.9) for the NPH group and 9,4 months (95% CI: 8.1-10.6) for the PH group. The median 1 year overall survival was 75% for NPH (95% CI: 0.70-0.81) and 71% for PH (95% CI: 0.59-0.85) ($p=0.441$) (Figure 2).

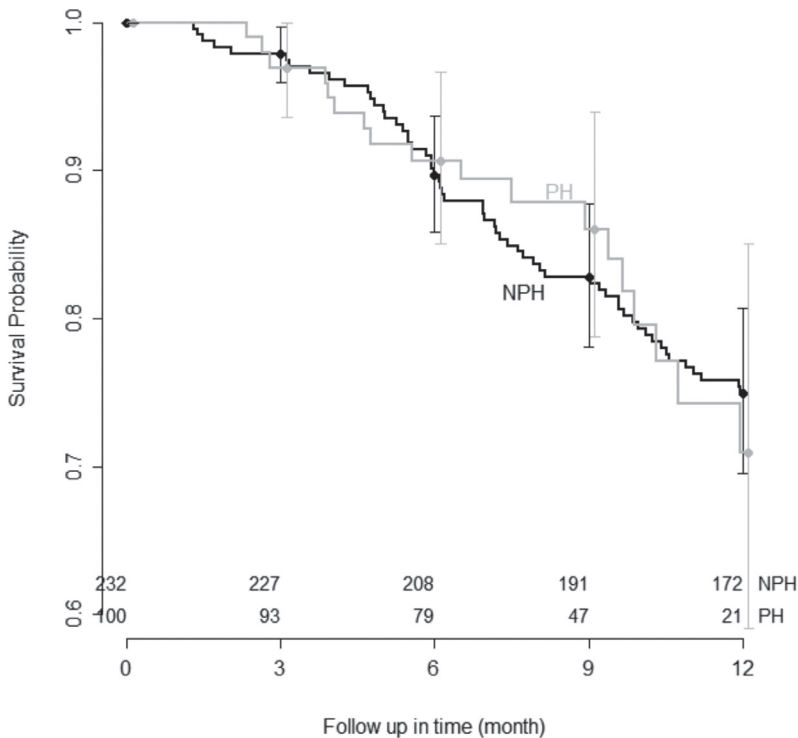


Figure 2. One year overall survival for NPH (n=232) and PH (n=100) patient groups.

Discussion

In this retrospective study, the clinical introduction of pre-hydration in daily dose cisplatin CCRT resulted in an improvement of treatment adherence due to a decrease in renal toxicity and an unexpected but clinically significant reduction of acute esophagitis.

Our results strongly suggest that this simple intervention indeed improves safety and compliance. This clinically relevant difference could not be

explained by other patient or treatment characteristics. Indeed, both groups were comparable in terms of all patient baseline and treatment characteristics but the increased exposure to cetuximab in the NPH group. However, the proportion of patients treated with cetuximab was relatively small and recent safety analysis did not show increased renal toxicity or acute esophagitis compared to CCRT alone in this cohort (19).

Halford et al. described the kinetics of cisplatin in patients with impaired renal function (20). When GFR was reduced to 60 ml/min, the AUC of cisplatin was larger, suggesting more exposure of cisplatin and thus more toxicity. However, the kinetics of low dose cisplatin has not been studied thoroughly. Publications on the sensitizing effect of cisplatin are focused on DNA adducts and the sensitizing effect and are not correlated with renal clearance (21;22). In contrary to carboplatin, no area under the curve is determined for cisplatin because of its nephrotoxicity. We therefore cannot prescribe an individualized dose and so prescribe to iso-toxicity levels. Based on our findings though, we can presume the correlation between renal clearance of cisplatin and toxicity. All pre-hydrated patients maintained a sufficient renal clearance over 60 ml/min. Prehydration on-demand, limited to patients who experience nephrotoxicity during the treatment is not as effective as prophylactic prehydration.

Intriguingly, PH was associated with a reduced rate of AET. Grade ≥ 2 toxicity was significantly reduced in the PH group. Several factors affect AET: 1) the employment of PH; 2) chemotherapy adherence and 3) radiotherapy dose. Further investigation is warranted to explain the actual changes in sensitivity of the esophagus to radiotherapy dose, chemotherapy and pre-hydration. Nijkamp et al recently analyzed the esophageal uptake of 18FDG after concurrent chemoradiation in patients without standard prehydration, reflecting the severity of esophagus toxicity (23). A follow-up study on PH patients might provide more insight in the hydration effect on the local dose to esophageal inflammation response.

One of the limitations is the uncontrolled design of the study. Although the only treatment change between patients treated in the NPH and the PH group was the application of pre-hydration, other unknown factors might have also influenced the outcome. Additionally, we did not adjust for multiple testing. This yields a higher false positive rate of our study. And an independent patient cohort is required to validate the findings of the study. However, the results are deemed to be reliable because of the number of patients and events and

comparability of the two cohorts. With regard to the efficacy, the short follow up of the PH patients is a limitation. However, the one year overall survival is thought to be a good surrogate marker for overall survival (24).

It would be interesting to analyze the actual mechanism of pre-hydration on organs at risk as well as tumors, when the follow-up of PH is long, or by setting up a clinical trial.

Although concurrent low dose cisplatin is not a standard regimen in non-small cell lung cancer, our findings are of clinical relevance. Because of its favorable toxicity profile and comparable survival outcome, more patients can benefit (25).

In conclusion, the clinical introduction of pre-hydration intervention was shown to reduce renal toxicity and increase chemotherapy adherence, and possibly reduce esophagus toxicity in patients with NSCLC treated with concurrent low dose cisplatin without influencing treatment efficacy.



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