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Original Article

Pre-hydration in cisplatin-based CCRT: Effects on tumour concentrations and treatment outcome

Else A. Aalbersberg [a,*,2], Maddalena M. Rossi [b,2], Linda J. de Wit – van der Veen [a], Iris Walraven [b], Michel M. van den Heuvel [c,1], Jan-Jakob Sonke [b], Jose S. Belderbos [b], Wouter V. Vogel [a,b]

[a] Department of Nuclear Medicine, Netherlands Cancer Institute; [b] Department of Radiation Oncology, Netherlands Cancer Institute; and [c] Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands

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ABSTRACT

Aims: Pre-hydration is routinely applied to reduce nephrotoxicity in concurrent cisplatin-based chemo-radiotherapy (CCRT). However, pre-hydration may also have systemic effects, potentially leading to lower tumour cisplatin concentrations. We investigated the impact of pre-hydration on tumour cisplatin concentrations in mice, and on treatment outcomes in a clinical cohort study.

Materials and methods: Four groups of 20 mice received either no pre-hydration prior to full-dose (6 mg/kg) or half-dose cisplatin, overnight dehydration prior to full-dose cisplatin (dehydration), or NaCl intraperitoneally prior to full-dose cisplatin (pre-hydration). Kidney function and tumour platinum concentration were measured. In patients, a retrospective study compared 2 historical NSCLC cohorts which received CCRT with daily cisplatin, with and without standard pre-hydration. Overall survival (OS) and progression free survival (PFS) were compared using Kaplan–Meier and cox-regression.

Results: Pre-hydration significantly decreased cisplatin tumour concentrations in mice, comparable to mice receiving half the dose. In 419 patients (211 without and 208 with pre-hydration) with median follow-up 22 months, there were no significant differences in PFS (18 vs. 15 months) or OS (23 vs. 23 months).

Conclusion: Pre-hydration reduces cisplatin tumour concentrations in mice, but it does not compromise treatment outcomes in NSCLC patients treated with daily cisplatin and radiotherapy.

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Concurrent chemo-radiotherapy (CCRT) is the current standard of care for patients with locally advanced non-small cell lung cancer (NSCLC). When compared to sequential chemoradiation, CCRT has been shown to lead to an OS of 5.7% after 3 years and 4.5% after 5 years, and to increase loco-regional control [1]. The type of chemotherapy used during CCRT does matter. In a recently published phase 3 trial in 200 patients two types of chemotherapy regimens were compared. It seemed that Carboplatin Taxol had a lower OS, and higher pulmonary toxicity compared to Cisplatin-Etoposide [2].

The main drawback of adding cisplatin concurrent to radiotherapy is the increase of toxicities, such as radiation oesophagitis, nausea, and bone marrow depression [1,3,4]. In addition, the use of platinum-based chemotherapeutic drugs comes with significant risk of temporary or persistent renal toxicity, which is considered an important dose-limiting factor [5]. This toxicity is primarily caused by accumulation of cisplatin in the proximal tubules [6].

One strategy to reduce the risk on cisplatin-induced renal toxicity is the application of hydration regimens, which has become standard of care for high-dose cisplatin administrations [7]. Other strategies are to reduce the dose of cisplatin per administration, while increasing the frequency of administrations to weekly or daily to achieve an adequate total dose or to use Carboplatin instead of Cisplatin [8,9]. Concurrent chemo-radiotherapy with daily low-dose cisplatin is generally well-tolerated, but about 20% of patients do not complete all of the 24 administrations due to toxicity [10]. Subsequently, efforts were made to mitigate renal toxicity by combining daily low-dose cisplatin with daily pre-hydration as standard practice for all chemoradiation NSCLC patients. This not only resulted in fewer patients being unable to complete the cisplatin administrations due to renal toxicity, but unexpectedly also reduced the grade ≥2 acute oesophageal toxicity from 62% to 34% [11]. This suggests that hydration not only has a local effect on the kidneys, but also a systemic effect. This led us to question whether pre-hydration could affect the kinetics of

* Corresponding author at: Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands.
E-mail address: e.aalbersberg@nki.nl (E.A. Aalbersberg).
[1] Present address Department of Pulmonary Medicine, Radboud University Medical Center, Geert Grooteplein Zuid 10, Nijmegen, the Netherlands.
[2] Shared first author.

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the cisplatin, with respect to normal tissues as well as in the tumour, and with potential consequences for treatment efficacy.

The aim of this study was to evaluate the impact of pre-hydration on tumour cisplatin concentrations and on treatment outcomes, by investigating its effects in (1) a pre-clinical in-vivo setting in mice and (2) in retrospective cohorts of NSCLC patients.

Methods and materials

Pre-clinical evaluation

Eighty female seven-week old FVB mice were transplanted with a BRCA1- and p53-deficient tumour [12] in the fourth right mammary fat pad under isoflurane anaesthesia. Rimadyl was given for pain relief during surgery and repeated after 24 h. Tumour growth was evaluated 3x per week by calliper measurements. When the tumour diameter reached 10 mm, the mice were divided equally into 4 treatment groups ($n = 20$): (1) free access to water followed by high-dose 6 mg/kg cisplatin iv (full-dose), (2) free access to water followed by 3 mg/kg cisplatin iv (half-dose), (3) overnight fasting from water followed by 6 mg/kg cisplatin iv (dehydration), and (4) free access to water followed by 1 ml 0.9% NaCl intraperitoneally 1 h prior to 6 mg/kg cisplatin iv (pre-hydration).

Renography

To evaluate renal toxicity scintigraphic renography was performed using ^{99m}Tc-MAG3, reflecting tubular function [13]. Five mice in each group underwent renography at 1, 24, 72, and 168 h after cisplatin administration to determine the effect of cisplatin on kidney function at different time points. Mice were placed under anaesthesia with 1.5–2.5% isofluorane on the NanoSPECT (Mediso, Hungary). 30 MBq of ^{99m}Tc-MAG3 was injected in the tail vein. A dynamic scan was made for 30 min with 10 second time-frames using a parallel-hole collimator. Immediately after scanning the mice were sacrificed and the tumour was resected. The time to reach maximum tracer uptake in the kidney (T_{max}) and the time to reach clearance to 50% of the maximum tracer uptake ($T_{halfmax}$) were determined as measures for renal function.

Cisplatin tissue concentrations

Tumour platinum concentrations were determined through the nitric acid digestion method, as described by Siddik et al. [14]. In short, 100 mg of tissue was dried overnight and dissolved in pure nitric acid (HNO_3). The nitric acid was subsequently evaporated through heating and the sample was diluted in 1 M hydrochloric acid (HCl). Heating and evaporation were repeated and the sample was diluted in 0.1 M HCl. Finally the samples were heated and evaporated and dissolved in a buffer solution containing 0.15 M NaCl and 0.2 M HCl. Platinum concentrations were measured with graphite furnace – atomic absorption spectrometry (SOLAAR MQZ Zeeman from Thermo Optek), GF95 graphite furnace and FS95/97 autosampler (Thermo Elemental).

Statistics for pre-clinical evaluations

Differences between groups in tumour concentrations and renal function were determined using median tests. Bonferroni correction was used to determine which groups differed significantly from each other. Analyses were performed in SPSS (v22.0.0.0, IBM Corporation). Graphs were plotted in GraphPad Prism (v7.03, GraphPad Software Inc.). $P < 0.05$ was considered significant.

Clinical evaluation

Since tumour cisplatin concentrations are difficult to determine invasively in patients, a retrospective study was performed comparing 2 patient cohorts treated with and without standard pre-hydration. All patients with cytologically or histologically proven locally advanced NSCLC treated between 2007 and 2013 with concurrent daily-low dose cisplatin only and radiotherapy in our institute were included in this retrospective study. Patients treated between 2007 and 2010 did not receive standard pre-hydration (PH−); patients treated between 2011 and 2013 received daily 1 litre pre-hydration (PH+) before each Cisplatin administration. Approval from the ethics committee was not required for this retrospective study.

Cisplatin and saline administration

All patients were prescribed daily low-dose cisplatin (6 mg/m^2 with a maximum of 12 mg total) intravenously, administered 1–2 h prior to radiotherapy as a bolus injection of 10 ml. Patients in the PH− group only received pre-hydration when they demonstrated a $\geq$20% increase in serum creatinine during treatment. Patients in the PH+ group received standard pre-hydration from fraction 1 onwards. Serum creatinine (SC), urea (U) and glomerular filtration rate (GFR) were assessed prior to treatment and twice weekly during treatment in order to monitor dehydration and renal problems according to standard clinical protocol. Serum thrombocytes, leucocytes, Hb, sodium, potassium and magnesium were evaluated with the same frequency. Pre-hydration consisted of 1.0 litre of saline (0.9%) administered prior to cisplatin, with the exception of patients with a history of cardiac failure or the occurrence of the syndrome of anti-diuretic hormone secretion (SIADH), these patients received 0.5 litre of saline. For all patients, cisplatin was discontinued if SC increased by $\geq$30% from baseline or the GFR decreased to $\leq$60 ml/min [11].

Radiotherapy

All patients were prescribed a dose of 66 Gy in 24 daily fractions (2.75 Gy per fraction) with an overall treatment time of 32–34 days. Patients received contrast-enhanced planning 4DCT from which a mid-position 3D planning CT was derived with the tumour in its time-averaged position [15]. A recently acquired ^{18}F-FDG PET/CT scan was registered to the planning 3DCT to assist with tumour delineation. Gross tumour volume and pathological lymph nodes were delineated (GTV) and subsequently expanded with a margin of 12 mm + ¼ tumour peak-to-peak amplitude for the tumour, and with 12 mm for the lymph nodes, to provide the planning target volume (PTV). The planning CT was then also used to delineate the organs at risk and for dose calculation. A 7–8 field IMRT plan was generated using 6 or 10 MV photons (Pinnacle Radiation Oncology Systems, Milpitas, USA). All plans were generated with a physical dose constraint on the oesophagus of V35 < 65% [16]. Patient setup correction was based on Cone beam CT (CBCT) for the first 3 fractions and then weekly thereafter until January 2012 then daily thereafter. Post treatment follow-up was performed according to standard clinical protocol by either the radiation oncologist or the (referring) pulmonologist at 1, 3 and 6 weeks, then at 3 monthly intervals up to 2 years, twice a year in the following year, and then yearly. This involved toxicity scoring, chest X-ray and/or CT scans and blood tests. Survival was measured up to August 2016.

Statistics for clinical evaluations

Normal distribution of the data was tested, and in case of non-normality, data were categorized in quartiles. All data are

presented as a percentage of the total; in case of normal distributed data as mean (±standard deviation), otherwise as median (interquartile range; IQR). Differences between the two groups were evaluated with either a *t*-test or chi-square test (for categorical variables). OS was calculated in months from the start of therapy to the date of the last follow-up (censored) or death from any cause. PFS was calculated from the start of treatment to the first recurrence or death from any cause, or last follow-up date (censored). Both PFS and OS were cut-off at 60 months to better compare the historical cohorts. Kaplan-Meier curves were plotted and differences in OS and PFS between the PH+ and PH− groups were assessed with cox regression analysis. Consequently, we tested the potential influencing effect of clinical characteristics that showed to be significantly different between the two groups at baseline, by adding them to the univariate model. When the variable changed the association between PH+ and OS/PFS >10% in hazard ratio (HR), the variable was kept in the model. All analyses were performed in SPSS (v22.0.0.0, IBM Corporation). Graphs were plotted in GraphPad Prism (v7.03, GraphPad Software Inc.). $P < 0.05$ was considered significant.

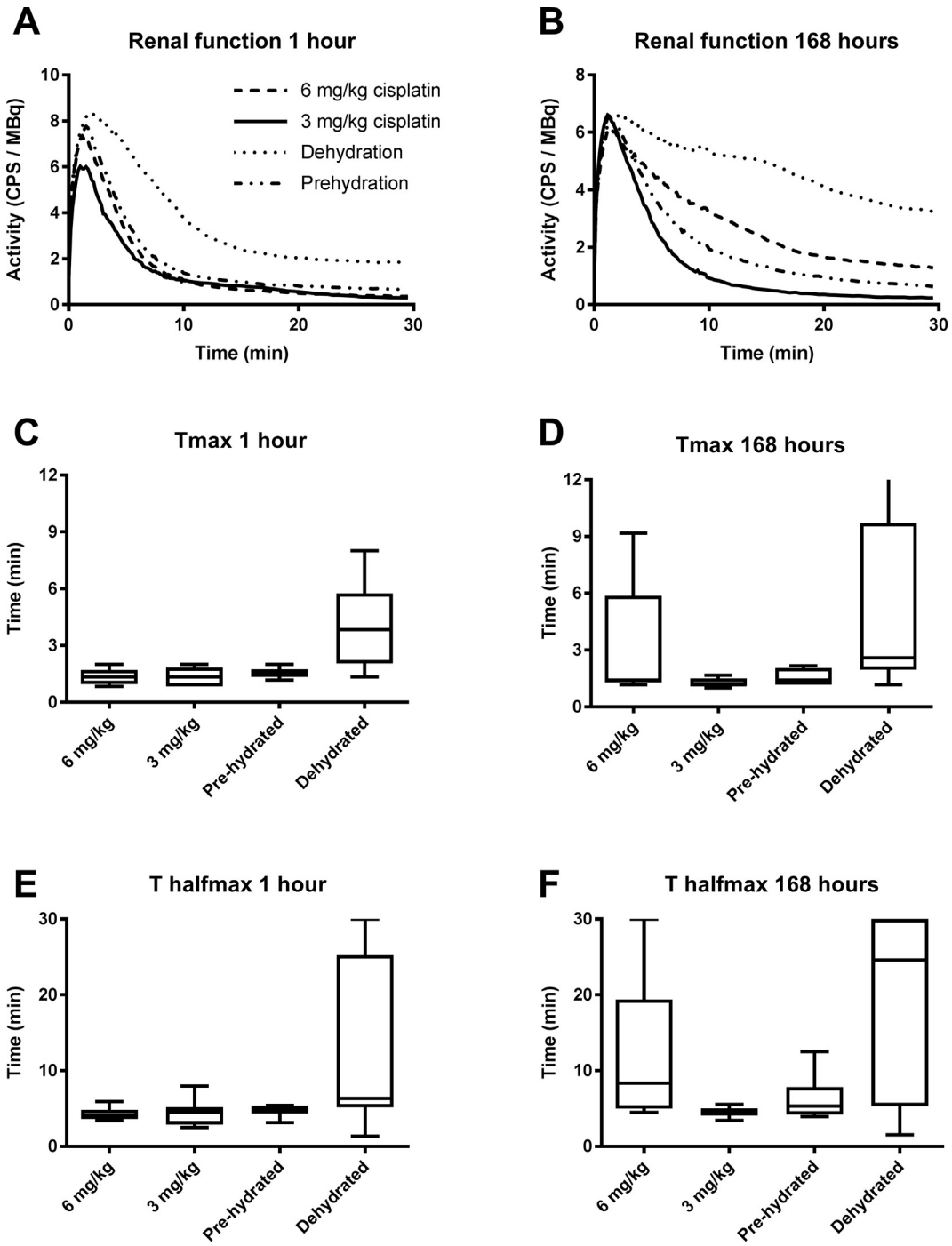

Fig. 1. Renography results after administration of cisplatin. The first row (A and B) shows averaged renography for 5 mice at 1 and 168 h post-injection of cisplatin. The time to reach the maximum uptake (Tmax) is quantified and shown in C and D. The time to reach the half of the maximum uptake (Thalfmax) is quantified and shown in E and F. 6 mg/kg = mice receiving a full-dose of 6 mg/kg cisplatin. 3 mg/kg = mice receiving a half-dose 3 mg/kg of cisplatin. Pre-hydrated = mice pre-hydrated with 1 ml of saline prior to a full dose of 6 mg/kg cisplatin. Dehydrated = mice dehydrated overnight prior to a full-dose 6 mg/kg cisplatin.

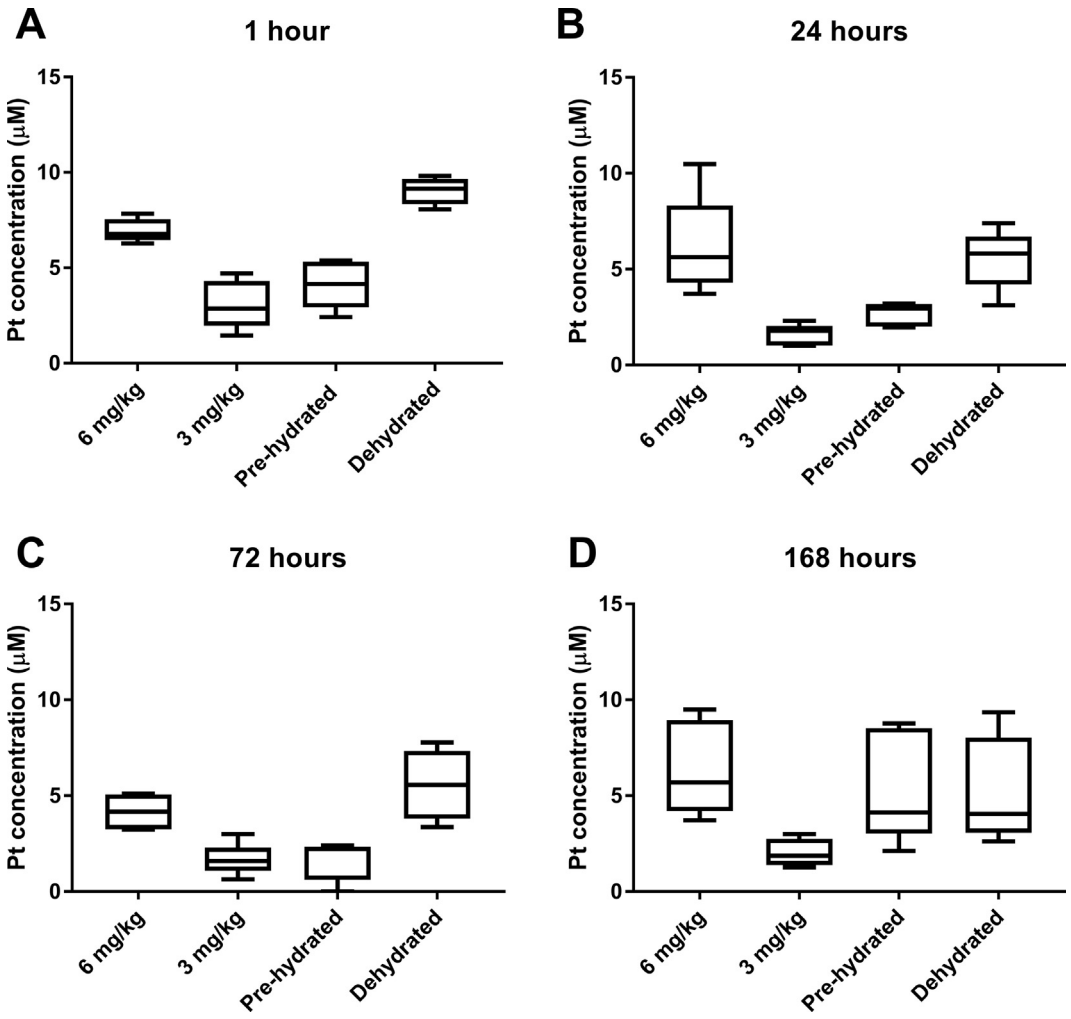

Fig. 2. Tumour cisplatin concentrations 1 (A), 24 (B), 72 (C), and 168 (D) hours post-injection of cisplatin. 6 mg/kg = mice receiving a full-dose of 6 mg/kg cisplatin. 3 mg/kg = mice receiving a half-dose 3 mg/kg of cisplatin. Pre-hydrated = mice pre-hydrated with 1 ml of saline prior to a full dose of 6 mg/kg cisplatin. Dehydrated = mice dehydrated overnight prior to a full-dose 6 mg/kg cisplatin.

Results

Renal function in mice

The results of renal function evaluations are shown in Fig. 1. The dehydration group showed highly variable but significant function loss at one hour after cisplatin administration: T_{max} was delayed to a median of 3.8 min (range up to 8.0 min) as compared to the other groups (full-dose 1.3, half-dose 1.3, pre-hydration 1.5 min). $T_{halfmax}$ was delayed to a median of 6.4 min (range up to 30 min) as compared to the other groups (full-dose 4.1, half-dose 5.0, pre-hydration 4.5 min), see Fig. 1b and 1c. Similar patterns were seen for dehydrated mice at evaluations up to 168 h after administration of cisplatin, see Fig. 1d and e. This illustrates the ability of renography to detect renal toxicity, as expected to occur in dehydrated mice receiving 6 mg/kg cisplatin. This also shows that this animal model mimics the clinical situation in which renal failure after cisplatin can be prevented with hydration and that there is inter-individual variation.

In normal hydrated mice, renal toxicity occurred depending on the administered cisplatin dose and was variable amongst individual mice, and this was best detectable at 168 h after administration: For 3 mg/kg cisplatin both median T_{max} and median $T_{halfmax}$ remained unaffected up to 168 h. For 6 mg/kg cisplatin median T_{max} was 1.3 min at 1 h (range up to 2.0 min) but increased in some of the animals leading to a median of 1.4 min after 168 h but with a much higher range up to 9.2 min. Median $T_{halfmax}$ was 4.1 min at 1 h (range up to 5.9 min) and increased to a median of 8.0 min after 168 h (range up to 30.0 min). This confirms that cisplatin-induced nephrotoxicity is dose-dependent and develops in the course of days.

Pre-hydrated mice receiving 6 mg/kg cisplatin showed limited renal toxicity: T_{max} remained within normal range with a median of 1.5 min at 1 h (range up to 2.0 min) and a median of 1.4 min after 168 h (range up to 2.2 min). $T_{halfmax}$ remained within normal range with median 4.5 min at 1 h (range up to 5.4 min), and showed a slight increase above the median of 6.0 min after 168 h (range up to 12.5 min) but this is significantly less than the median 8.0 min (range up to 30 min) as reported in normally hydrated mice. This confirms that pre-hydration can protect against cisplatin-induced nephrotoxicity.

Tumour cisplatin concentrations in mice

Fig. 2 shows the cisplatin concentrations in harvested tumour as measured at 1, 24, 72 and 168 h after administration. Compared to normally hydrated mice (6 mg/kg), pre-hydrated mice demonstrated a significantly lower median cisplatin concentration in tumours at 1, 24, and 72 h, but this difference was no longer present after 168 h. Given the known renal function loss in this

group, this illustrates that lower renal clearance of cisplatin leads to a higher accumulated dose in tumour in the clinically relevant window of the first hours after administration.

Normally hydrated mice showed cisplatin concentrations in tumour according to administered dose: Median 6.8 μM in the 6 mg/kg group versus 2.9 μM in the 3 mg/kg group, at one hour after administration. This difference remained significant 24 and 72 h after administration. This illustrates the ability of the performed analysis to quantify tumour concentrations over time.

Pre-hydrated mice receiving 6 mg/kg cisplatin consistently showed significantly lower tumour concentrations as compared to normally hydrated mice receiving the same dose: 4.2 μM versus 6.8 μM at the clinically relevant time point of 1 h after administration. The tumour concentrations of 4.2 μM achieved in the full-dose (6 mg/kg) normally hydrated group approached the 2.9 μM achieved in the half-dose (3 mg/kg) normally hydrated group (difference not significant). This pattern remained similar until 168 h after administration, although differences diminished over time and lost significance. This indicates that pre-hydration has systemic effects, and results in significantly lower cisplatin concentrations in tumour in the clinically relevant window of the first hours after administration.

Patient cohort study

419 patients were included in the analysis, 211 in the PH− group and 208 in the PH+ group. The median follow-up for the whole cohort was 22 months, and for the PH− and PH+ groups 23 and 22 months respectively. Baseline and treatment characteristics are shown in Table 1. Patients treated in the PH− group had a poorer performance status (WHO 1–2 in 67.0% vs. 53.6%, $p = 0.006$) compared to patients treated in the PH+ group. Furthermore, there was a difference in histological subtypes between the two groups ($p = 0.001$). There was a higher percentage of patients in the PH− group who were unable to complete their cisplatin regimen, 30.4% vs. 12.6% in the PH+ group leading to a difference in number of cycles of cisplatin received ($p < 0.003$). No other significant differences were found between the two groups.

Renal function in patients

Mean baseline GFR (94.78 ± 23.02 vs. 97.77 ± 23.30, $p = 0.22$) and U (6.50 ± 9.22 vs. 5.04 ± 1.61, $p = 0.056$) were similar in the PH− and PH+ groups, while baseline SC (73.60 ± 16.03 vs. 69.51 ± 15.94, $p = 0.006$) was slightly increased in the PH− group. The maximum absolute decrease in GFR was significantly more in the PH− group (−22.96 ± 20.67 vs. −11.97 ± 13.21, $p < 0.001$), and the maximum absolute increase in SC (25.74 ± 70.41 vs. 9.17 ± 10.57, $p = 0.001$) and U (6.31 ± 14.88 vs. 2.25 ± 1.69, $p < 0.001$) were significantly higher in the PH− group.

Survival analysis in patients

No significant differences were found in OS and PFS between the PH− and PH+ groups. Fig. 3 shows the Kaplan–Meier curves for overall- and progression free survival, which were similar for PH− versus PH+ patients (23 vs. 23 months and 18 vs. 15 months, respectively). In univariate analysis, no association was found between pre-hydration and PFS (HR 1.021 CI 0.806–1.293) or OS (HR 0.935 0.741–1.180). Correction for potentially influencing factors performance status and histology did not significantly influence the association between pre-hydration and PFS and OS, whilst the number of cisplatin cycles changed the hazard ratio by 12%. However, the association between pre-hydration and PFS and OS remained insignificant (Table 2).

Discussion

We demonstrated for the first time that hydration prior to cisplatin administration in mice leads to significantly lower cisplatin concentrations in tumour up to 72 h post administration, comparable to giving only half the cisplatin dose without pre-hydration. While the relationship between pre-hydration and the conse-

Table 1
Patient characteristics of the total population and the groups receiving either no standard pre-hydration (PH−) or standard pre-hydration (PH+).

	Total population	Group PH− 2007–2010	Group PH+ 2011–2013	*p* value
Number of patients	419	211	208	–
Mean age in years (IQR)	62.0 (54–70)	62.1 (55–70)	61.8 (54–69)	0.780
Gender (%)				0.902
Male	245 (58.5)	124 (58.8)	121 (58.2)	
Female	174 (41.5)	87 (41.2)	87 (41.8)	
Performance status[a] (%)				0.006*
WHO 0	159 (39.5)	69 (33.0)	90 (46.4)	
WHO 1–2	244 (60.5)	140 (67.0)	104 (53.6)	
TNM (%)				0.203
1a–2b	25 (6.0)	16 (7.6)	9 (4.4)	
3a	227 (54.6)	112 (53.3)	115 (55.8)	
3b	164 (39.4)	82 (39.1)	82 (39.8)	
Histology[b] (%)				0.001*
AC	123 (31.5)	44 (23.3)	79 (39.3)	
SCC	123 (31.5)	65 (34.4)	58 (28.9)	
NSCLC NOS	112 (28.8)	68 (36.0)	44 (21.9)	
Other	32 (8.2)	12 (6.3)	20 (9.9)	
Metformin use (%)	32 (7.7)	17 (8.1)	15 (7.2)	0.734
Median GTV[c] in cc (IQR)	111 (65–207)	121 (74–204)	104 (57–212)	0.130
Median PTV[d] in cc (IQR)	566 (365–805)	576 (373–805)	526 (334–787)	0.776
FEV1[e] (IQR)	78 (64–93)	77 (60–91)	80 (66–93)	0.265
Median number of cisplatin cycles (IQR)	24 (24–24)	24 (20–24)	24 (24–24)	0.003*
GFR baseline[f] (IQR)	97 (81–111)	95 (81–105)	98 (81–112)	0.203

Missing values (if $N > 10$); [a]16, [b]29, [c]22, [d]185, [e]105, [f]87, TNM = TNM Classification of Malignant Tumours – 7th edition, AC = adenocarcinoma, SCC = squamous cell carcinoma, NSCLC NOS = non-small cell lung cancer not otherwise specified, GTV = gross tumour volume including lymph nodes, PTV = planning target volume, FEV1 = forced expiratory volume in 1 s, IQR = interquartile range.

* Indicates significant.

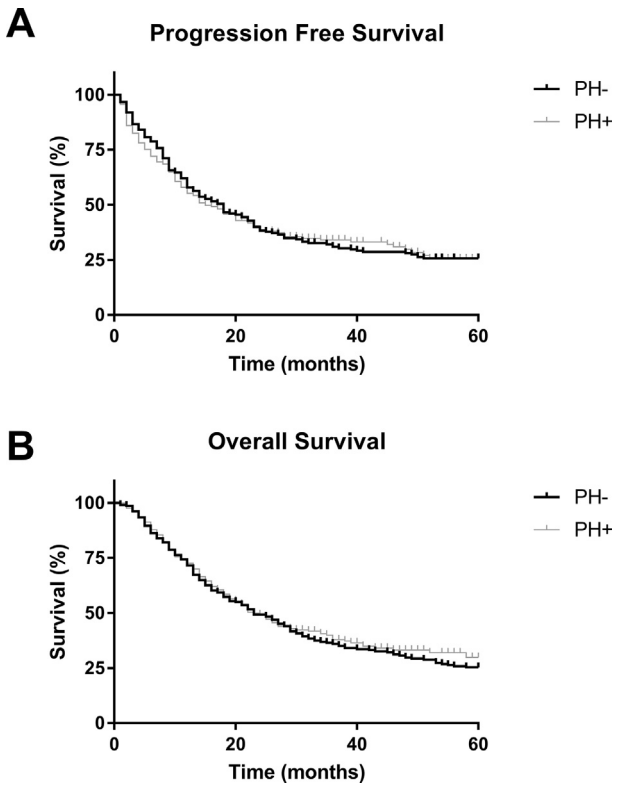

Fig. 3. Kaplan–Meier curves for (A) progression free survival and (B) overall survival. PH− group receiving no standard pre-hydration (thick black line). PH+ group receiving standard pre-hydration (thin grey line).

quently altered plasma pharmacokinetics of cisplatin have been described previously in rats [18–19], to our knowledge no other studies have investigated the relationship between pre-hydration and tumour cisplatin concentrations or between pre-hydration and survival, either in pre-clinical or clinical research.

Furthermore, we demonstrated for the first time in a clinical retrospective patient cohort that the administration of standard pre-hydration prior to daily cisplatin is not associated with reduced progression free or overall survival. There are several factors that can contribute to interpretation of these seemingly contradictory findings.

Pre-hydration

The results from the pre-clinical mouse study cannot be extrapolated directly to the patient cohort. In the animal study the maximum pre-hydration possible was given intraperitoneally prior to administration of one relatively high dose of cisplatin, whilst patients received rather modest pre-hydration with 1L of saline intravenously over 1 h prior to daily low-dose cisplatin. Nonetheless, pre-clinical results should be considered indicative of a potential effect of pre-hydration on cisplatin concentrations in human tumours.

Many different hydration administration protocols exist, depending (amongst others) on tumour type, cisplatin dosing schedule, patient comorbidities, and logistics [20]. Stronger pre-hydration, e.g. 3-4L saline intravenous per 24 h, is usually applied when renal function loss develops after high-dose cisplatin, or when limited pre-hydration provides insufficient protective effect [7]. It currently remains unknown whether such schemes can induce more extensive reductions in tumour cisplatin concentrations or can lead to measurable effects on treatment outcome parameters. The benefits of pre-hydration, however should not be disregarded. Pre-hydration is an effective strategy to prevent renal toxicity, as again demonstrated in this study with a reduced decrease in GFR and reduced increase in serum creatinine and urea. Patients in the cohort without standard pre-hydration would initiate the same pre-hydration scheme upon development of renal function loss. This will have diminished differences between the two groups.

Cisplatin concentrations

The animal model chosen in this study utilizes a one-time high dose of cisplatin. This model was chosen since this high-dose leads to measurable tumour cisplatin concentrations. The drawback is that this cannot be administered daily, comparable to the clinical situation. Although there are no indications that the pharmacokinetics of low-dose and high-dose cisplatin are different, the use of cumulative doses was not studied.

The question remains whether or not pre-hydration leads to altered cisplatin concentrations in tumour in patients. The pre-clinical study demonstrated that the pre-hydrated mice had lower tumour concentrations compared to dehydrated and normally hydrated mice receiving the same dose even up to a period of 168 h, whereas the normal and dehydrated groups had renal function loss and therefore less cisplatin clearance resulting in a higher concentration in the tumour. Assuming these same processes occur in humans, this indicates that pre-hydration does have a systemic effect and that the concentration in the tumour is clinically relevant in the first hours after administration. This can only be evaluated directly in patients using invasive evaluations. Still, there are indirect indications that pre-hydration does lower cisplatin concentrations in tissues. With the addition of cisplatin to radiotherapy, many studies have demonstrated an increase in acute normal tissue toxicity [21]. We observed reductions in these toxicities with the introduction of standard-pre-hydration, most notably of oesophageal toxicity, which supports the concept of reduced accumulation of cisplatin in normal tissues [11]. Whether this will go together with similar reductions in tumour concentrations remains hypothetical.

Survival outcomes

The benefit of concurrent chemoradiotherapy (CCRT) over sequential chemoradiotherapy alone in overall survival has been

Table 2
Hazard ratio and confidence interval for patients treated with standard pre-hydration (PH+) compared to patients without standard pre-hydration (PH−, reference).

	PFS			OS		
	HR	CI	*P* value	HR	CI	*P* value
Prehydration	1.021	0.806–1.293	0.87	0.935	0.741–1.180	0.57
Prehydration & PS	1.020	0.800–1.299	0.88	0.925	0.728–1.177	0.53
Prehydration & histology	0.978	0.762–1.256	0.85	0.970	0.758–1.241	0.97
Prehydration & cisplatin cycles	1.071	0.836–1.371	0.59	1.044	0.819–1.331	0.73

PS = performance status.

estimated at 10% at two years in patients with NSCLC [3]. If pre-hydration would have a negative effect on this overall survival benefit, it would probably be small. In this study we did not see an effect on overall survival. In general, the patients evaluated in our cohorts demonstrated good treatment outcome (23 months), comparable to those receiving standard dose CCRT without cetuximab in the RTOG 0617 trial (24 months) [22] and other trials [17].

There were some significant differences between the 2 patient groups that may have diminished differences in treatment outcomes. The group treated without standard pre-hydration had a lower average performance score which is associated with poorer local control and OS [23]. Tumour histology and number of received cisplatin cycles were also significantly different. Although these factors by themselves did not affect the hazard ratio of hydration >10%, and were therefore not corrected for, together they could have compensated for a potential negative effect of pre-hydration on tumour cisplatin concentrations and treatment outcomes.

Since 2012, we have changed our image guidance protocol from weekly to daily cone beam CT based corrections. This may have allowed a slightly better tumour coverage in the second half of the group receiving standard pre-hydration, potentially also diminishing differences in treatment outcome [24].

In summary, the presented pre-clinical evidence and clinical toxicity data support the hypothesis that pre-hydration reduces cisplatin concentrations in humans. This did not result in a detrimental effect on clinical outcome parameters of a detectable magnitude in the available retrospective cohorts treated with daily low-dose cisplatin and radiotherapy. It can however not be excluded that implementations of strong pre-hydration as performed in high-dose cisplatin may influence achieved tumour concentrations or treatment outcomes. This would need to be evaluated in prospective randomised clinical trials. However, as pre-hydration with daily low-dose cisplatin does not affect OS or PFS in this retrospective clinical study, we are continuing to use pre-hydration in our standard protocol due to its benefits for renal protection and patient treatment adherence.

Conclusion

Pre-hydration significantly decreases cisplatin tumour concentration in mice, comparable to administration of half a dose of cisplatin without pre-hydration. In a large cohort of patients with NSCLC treated with concurrent low-dose cisplatin and radiotherapy, pre-hydration appeared to have no detrimental effect on progression free- and overall survival.

Conflict of interest statement

The department of radiation oncology (MMR, IW, MMvdH, JJS, JSB, WVV) receives software license fees from Elekta Oncology Systems Ltd. Part of this research was funded from these licence fees. This research was partially funded by a Top sector Life Sciences & Health (LSH-TKI Foundation) public–private partnership grant (LSHM15036) in collaboration with Elekta Oncology Systems Ltd.

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