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A preliminary pharmacokinetic study of docetaxel, carboplatin and concurrent radiotherapy for regionally advanced squamous cell carcinoma of the head and neck

Luigi Cattel [a,*], Valeria Recalenda [a,1], Mario Airoldi [b], Valentina Tagini [a,2], Laura Delprino [a], Flavio Rocco [a], Cesare Bumma [b]

[a] *Dipartimento di Scienza e Tecnologia del Farmaco, Scuola di Specializzazione in Farmacia Ospedaliera, via Pietro Giuria 9, 10125 Turin, Italy*
[b] *Ospedale S. Giovanni Antica sede, Divisione di Oncologia Medica, ASL1, via Cavour 31, 10123 Turin, Italy*

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Abstract

This work investigates the pharmacokinetics and toxicity resulting from the concomitant use of low dose carboplatin (CBCA)/docetaxel (DTX) plus concurrent radiotherapy in patients with head and neck cancer. The study comprised 11 patients with stage III–IV head and neck cancer. All patients received 2 Gy radiotherapy daily, 5 fractions per week, up to a planned total of 70 Gy over 7 weeks. CBCA (AUC 0.4 mg/ml, min/day) was also administrated as 20 min i.v. infusion, starting 1 day before the first radiotherapy fraction. CBCA was administered for 5 consecutive days every 2 weeks (weeks 1, 3, 5 and 7). DTX 30 mg/m^2 (1 h i.v. infusion) was given as a single dose on days 10, 24 and 38. CBCA on day 1 and DTX on day 10 were analysed to determine the concentration–time curves during the first 24 h. CBCA C_{max} and C_{min} in 2–5 days and on day 15 and 29, as well as total plasma platinum on days 2, 3, 4, 5, 29 and 43 were also assayed. By calculating the non-compartmental pharmacokinetic parameters of the two drugs from the available plasma concentrations we found in the first week values similar to those reported in the literature as single agents. In contrast, during subsequent weeks (weeks 3 and 5), a significant and progressive increase of platinum levels was observed. So, it could be assumed that after 2 weeks of CBCA and DTX treatment a bias in dose calculation occurred because the linear relationship between creatinine clearance (used to calculate the expected AUC through the Calvert formula) and CBCA clearance was no longer observed.

Keywords: Pharmacokinetics; Docetaxel; Carboplatin; Head and neck cancer; Radiotherapy; Toxicity

1. Introduction

Carboplatin (CBCA) is an analogue of cisplatin and a number of randomised trials [1,2] have demonstrated that it has efficacy equal to that of cisplatin against various malignancies, including head and neck cancer. The dose-limiting toxicity for CBCA is myelosuppression (mainly thrombocytopenia), while nefrotoxicity is much lower than with cisplatin. Previous clinical studies suggested that a major determinant of CBCA myelotoxicity was plasma AUC for free platinum and that AUC was clearly dependent upon the renal excretion capability [3,4].

Docetaxel (DTX) is an analogue of paclitaxel that exerts its cytotoxic properties through the inhibition of microtubule depolymerisation and promotion of tubulin assembly [5]. In a phase II study, DTX has demonstrated various degrees of activity against melanoma, gastric cancer, urothelial cancer, soft tissue sarcoma, pancreatic cancer, small-cell lung cancer and head and neck cancer [6]. In comparison with paclitaxel, DTX pharmacokinetics is linear within the range of therapeutic doses.

The association of DTX and CBCA was recently investigated in patients with non-small-cell lung cancer

* Corresponding author.
E-mail address: cattel@pharm.unito.it (L. Cattel).
[1] Present address: Ospedale Civile and orfanotrofio di Asti, Servizio Farmaceutico, ASL 19, via orfanatrofio 15/17, 14100 Asti, Italy.
[2] Present address: Istituto per la ricerca e la cura del cancro (IRCC), Servizio di Farmacia, strada provinciale 142-Km 395-10060 Candiolo, Turin, Italy.

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(NSCLC), prostate cancer and ovarian cancer. This new association was better tolerated than that with paclitaxel or cisplatin, while maintaining the same activity [7].

CBCA has shown excellent radiosensitisation by inhibiting DNA repair. The combination of continuous infusion of CBCA (12 mg/m^2/day) and radiotherapy (2 Gy daily, up to a 60 Gy in 6 weeks) in advanced squamous carcinoma of the cervix uteri IIB–IIIB (UICC) resulted in relatively low toxicity. Since platinum at 12 mg/m^2/day had not reached the steady-state concentration in plasma, the authors suggested testing a schedule at 20 mg/m^2/day [8]. In a previous study, CBCA low-dose was safely used in a daily prolonged schedule, concomitant with conventional radiotherapy in patients with inoperable locally advanced head and neck cancer [9].

DTX has also shown excellent radiosensitisation through cell blockage in the G2-M phase. Studies conducted in vitro have shown that combining DTX with CBCA enhances the effects of radiation more effectively than either drug separately [10,11]. In a phase I/II study with concomitant radiotherapy for NSCLC, radiosensitisation with DTX was shown to be feasible; the recommended dose was 30 mg/m^2/week [12]. In another phase I study, the MTD dose was 20 mg/m^2/week with concomitant radiotherapy (60 Gy total) for 6 weeks. The dose-limiting toxicity was neutropenia, esophagitis and lymphopenia [13].

In the present research, applying doses and schedules reported in previously published works [9,12,13], the pharmacokinetics of CBCA and DTX administered at low doses as radiosensitiser was investigated (CBCA AUC = 0.4 min·mg/ml and DTX 30 mg/m^2) with concomitant fractionated radiotherapy. A possible relationship between pharmacokinetics, preliminary toxic effects and clinical efficacy was also investigated.

2. Materials and methods

2.1. Patients and treatment plan

Patients with histologically confirmed stage III–IV head and neck cancer were eligible for the study. Other eligibility criteria included: disease not susceptible to first-line surgical removal, absence of distant metastases, age below 70 years, Estern Cooperative Oncology Group (ECOG) performance status ≤ 2, no evidence of major alterations of hepatic, renal or cardiac function at the time of the study.

2.2. Radiotherapy

Patients underwent dental/oral surgical evaluation before radiotherapy. Radiotherapy was started 7–10 days after tooth extraction. A feeding tube was considered if nutritional status was compromised. All patients received 2 Gy radiotherapy daily, 5 fractions per week, up to a planned total of 70 Gy in 7 weeks. The boost volume included tumour plus a 2 cm margin of the anatomic compartment. An electronic beam was used to treat the neck tumoural node when deemed appropriate.

2.3. Chemotherapy

CBCA was administered as a 20-min i.v. infusion from day 1–5 of weeks 1, 3, 5 and 7. CBCA was calculated at a dose adjusted for renal functions to achieve a target AUC of 0.4 using the Calvert formula [4] with 24 h creatinine clearance (Ccr) as substitute for glomerular filtration rate (GFR): dose (mg) = AUC × (Ccr + 25). DTX (30 mg/m^2) was administered as a 1 h i.v. infusion on days 10, 24 and 38.

2.4. Premedication

All patients received the following medications: antiemetic therapy (metoclopramide), antimicotic treatment (itraconazol) of oral cavity and steroid medication (dexamethasone).

2.5. Toxicity

Toxicities were defined according to the WHO toxicity scale. Chemotherapy was suspended if patients presented grade 4 mucositis, or grade 3 mucositis lasting for more than 7 days, or WBC count $< 1500/\mu l$, or platelets count $< 50\,000$.

2.6. Pharmacokinetic study design

Blood samples for analysis were obtained at the following times: on day 1, before CBCA infusion, at the end of CBCA infusion, 20, 40, 1 h 40 and 4 h 40 min after the end of CBCA infusion; on the following 4 days of the first week and on the 1st day of weeks 3, 5 and 7, at the end of CBCA infusion and 4 h 40 min after the end of CBCA infusion; on day 10 before DTX infusion, at the end of DTX infusion, 15, 45 and 1 h 20 min after the end of DTX infusion.

Blood samples were collected in heparinised tubes for CBCA analysis or in tubes containing potassium edetic acid for DTX, from a large vein in the arm not receiving the drug infusion. Plasma was separated by centrifugation (10 min, 2000 × g), a portion was stored at -20 °C until analysis and the remainder was processed for ultrafiltration following a previously described procedure [14].

The trial and its pharmacokinetic amendments were approved by the Ethical Committee of the 'S. Giovanni

Antica Sede' Hospital, Turin, Italy. All patients gave their witnessed informed consent, as required by Italian law.

In order to calculate pharmacokinetic parameters, we used non-compartmental modelling approaches utilising the KINETICA 2000™ software (Innaphase, France).

The reference material was supplied by Bristol–Myers Squibb (Paraplatin, Italy) and by Rhone Poulenc (Taxotere, Antony, France). Deionised water, obtained by the Milli-Q plus system (Millipore S.A., Molsheim, France) was used throughout. Argon and nitrogen gas, Triton X-100 (BDH Ltd, Poole, England), hydrochloric acid (37%) and sodium chloride, acetonitrile, methanol and phosphoric acid (Merck, Darmstadt, Germany) were used as purchased. Pt- and docetaxel-free plasma originating from healthy volunteers was used.

2.7. Carboplatin analysis from plasma samples

A 3030-Z Zeeman spectrometer, equipped with a AS-60 autosampler (Perkin–Elmer, Norwack, USA) was used. The Pt hollow-cathode lamp (Perkin–Elmer) operated at a voltage of 30 mV. The pyrolytically-coated partitioned graphite tubes (Perkin–Elmer) were routinely replaced after approximately 100 firings. Platinum levels were quantified using a validated method based on Zeeman atomic adsorption spectrometry and were recalculated as CBCA [14].

2.8. Docetaxel analysis and plasma extraction

An HPLC system consisting of a Shimadzu LC-10ADvp pump and a Shimadzu SPD-10Avp UV spectrophotometer was used. The analytical column was a stainless-steel tube Symmetry C_{18} (250 × 4.6 mm i.d.), with a Symmetry C_{18} precolumn (Waters).

DTX was determined using an UV detector at a fixed wavelength of 229 nm. DTX was assayed in plasma using the above-described HPLC system with a solid-phase extraction, as described elsewhere [15].

3. Results

3.1. Pharmacokinetics

The pharmacokinetics of CBCA and DTX was investigated in 11 patients. Fig. 1 shows the concentration–time curve for the plasma UF of a single patient treated with CBCA AUC 0. 40 min·mg/ml 20 min i.v. infusion during the 1st day and that of DTX in a patient treated with 30 mg/m^2 of drug on day 10. The C_{max} plasma level of CBCA in 11 patients ranged from 3361–2044 ng/ml (at 20 min), whereas C_{min} was reached 5 h after i.v. bolus 250–500 ng/ml. Thus, 80–90% of CBCA was cleared from the plasma 6–8 h after i.v. administration. The CBCA plasma concentration was measured as ultrafiltrable free platinum by atomic adsorption spectrometry. It was found that ultrafiltrable platinum in the first 12–24 h consisted almost entirely of unchanged drug, showing that ultrafiltrable platinum level may be a useful guide to determine unchanged CBCA level in plasma [3,16,17]. C_{max} and C_{min} plasma values of DTX, taken on day 10, showed a marked intervariability among patients. The C_{max} usually ranged around a value of 1 mg/ml (mean value 0.735 mg/ml) which corresponded to the C_{max} recently reported [18]: starting from DTX 1 h i.v. infusion these authors found a mean value of 2.6 mg/ml.

Table 1 summarises the main pharmacokinetic parameters obtained from non-compartmental analysis of CBCA on day 1 and of DTX on day 10. These values were similar to those previously reported in the literature for ultrafiltrable plasma CBCA [19–21]. The mean observed AUC values and the target AUC value for each patient predicted by the Calvert formula were near the mean coefficient of variation was ± 10%.

Table 2 summarises CBCA C_{max} and C_{min} at weeks 1, 3 and 5. During the first week, on days 2, 3, 4 and 5, we noted no significant increase of C_{max} CBCA concentration. By measuring the C_{max} at the beginning of the subsequent courses of therapy (i.e. weeks 3 and 5), we noted a significantly increase in C_{max} of 7.2% on day 15 and 24% on day 29, whereas no substantial variation in C_{min} values was found.

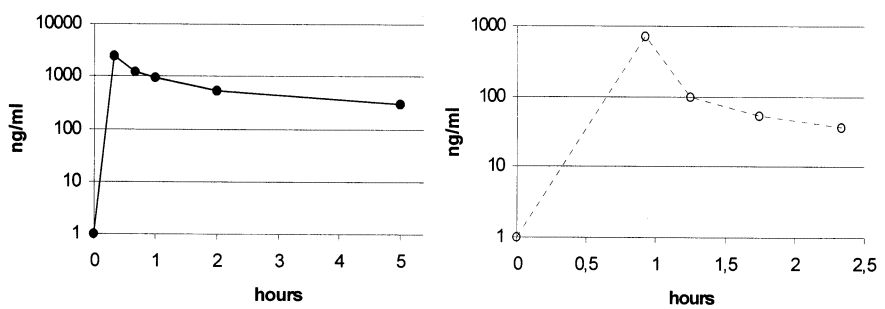

Fig. 1. Plasma UF concentration–time curve for CBCA and DTX obtained in a patient.

Table 1
Pharmacokinetic parameters of CBCA and DTX

Pharmacokinetic parameters	CBCA (nine patients)		DTX (nine patients)	
	Mean values	SD	Mean values	SD
C_{max} (ng/ml)	2702.2	658.6	734.94	396.23
AUC (h*ng/ml)	6868	1512	1088	526
Ke (h^{-1})	0.35	0.08	3.00	1.28
$t_{1/2}$ (h)	2.09	0.45	0.94	0.65
MRT (h)	2.94	0.73	1.25	1.00
Vp (l)	21.08	6.8	113.30	87.42
Vz (l)	21.68	6.89	125.20	96.72
Cl (l/h)	7.24	1.91	65.14	24.45

Non-compartmental parameters were estimated using the software KINETICA™ 2000.

Table 2
UF plasma levels of CBCA during days following the first one

Day of treatment	C_{max} (ng/ml ± SD)	P	C^*_{min} (ng/ml ± SD)	P
1	2664 ± 564		505 ± 282	
2	2596 ± 855	n.s.	487 ± 394	n.s.
3	2552 ± 681	n.s.	503 ± 310	n.s.
4	2768 ± 1104	n.s.	426 ± 155	n.s.
5	2717 ± 1375	n.s.	437 ± 148	n.s.
15	2856 ± 402	0.05	443 ± 110	n.s.
29	3316 ± 399	0.02	425 ± 377	n.s.

Data represent the mean values in seven patients ± SD. The statistical significance was determined by Mann–Whitney test. n.s., statistically not significant ($P\alpha < 0.05$).
*C_{min}, concentration after 5 h from the beginning of CBCA infusion.

We also studied the levels of total plasma platinum on days 2, 3, 4 and 5 during the first course of Pt administration (week 1) consisting mainly of protein-bound platinum (usually bound irreversibly to albumin and erythrocytes): the total Pt concentrations rose from 50 to 200 ng/ml from day 2 to day 4. These data are in agreement with many studies that have reported that a steady-state plasma level was not reached for total platinum [22], since CBCA slowly irreversibly bound to the plasma protein (up to 87% after 24 h) and free platinum cleared rapidly after 24 h [23]. We observed a value of 40 ng/ml of total platinum also on the 1st day of weeks 3 and 5, suggesting that during each course of × 5 days of CBCA therapy the total platinum continuously rose without reaching a steady-state level [22].

3.2. Preliminary response and toxicity

In a preliminary study, the complete and partial response rates following WHO criteria were 64% (7 out of 11 patients) and 9% (1 out of 11), respectively, for a total response rate of 73% (8 out of 11). Three patients (27%) had a progressive disease.

Mucositis was the most common seen and significant adverse effect, with three patients showing grade 4 and five showing grade 3 toxicity. Grade 4 mucositis generally occurred between week 5 and week 7. Chemotherapy was suspended with grade 4 mucositis or with grade 3 mucositis lasting for more than 7 days. Haematological toxicity was generally very modest (grade 1 or 2). The single exception was a patient simultaneously affected by grade 4 thrombocytopenia and grade 4 mucositis.

4. Discussion

The aim was to study the non-compartmental pharmacokinetic parameters of CBCA and DTX in concurrent radiotherapy in order to evaluate the effective patient exposure to the drugs and the safety of this regimen.

Apparently no pharmacokinetic interactions were seen between CBCA and DTX even under concomitant radiotherapy. The values of the non-compartmental pharmacokinetic constants for the two drugs at the beginning of treatments (CBCA on day 1 and DTX on day 10) were similar to those reported in the literature for the drugs used as single agents [15,19–21,24].

Nevertheless, there was some difference between pharmacokinetic constants observed at the beginning of each course (× 5 days) of therapy with CBCA and after the subsequent repeated treatments. During the first course of chemotherapy, the values of experimental AUC and those calculated using the Calvert formula were near, with a coefficient of variation of 10% for each patient. The C_{max} CBCA plasma level also remained constant after repeated administration for 5 days. In contrast, during subsequent weeks (weeks 3 and 5), a significant and progressive increase of platinum levels was observed. Analogously, some authors noted an increase of up to 70% in the UF AUC with repeated courses of cisplatin [25]. Nevertheless, CBBCA is much less nephrotoxic than cisplatin, so the increase of C_{max} CBCA observed during repeated courses could hardly be explained by a decrease in renal clearance. Alternatively it could be assumed that a bias in dose calculation occurred because of a non-linear relationship between Ccr (used to calculate the expected AUC through the Calvert formula) and CBCA clearance. It has been suggested that Ccr may not be a reliable measure of GFR and that more precise methods should be explored [26,27].

In this preliminary report the protocol appeared well tolerated by the patients, albeit grade 4 mucositis occurred in three patients.

The complete response rate observed in 7/11 patients is quite encouraging, and may highlight the radiosensitising effect of CBCA and DTX in combination.

The study will continue with a larger number of patients to substantiate the observed initially clinical efficacy, as well as to establish more clearly the significance of variations in free and bound Pt after repeated courses of CBCA administration.

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