Journal of BUON **15:** 297-302, 2010

ORIGINAL ARTICLE

Monitoring levels of nephrotoxicity of different aminoglycosides during febrile neutropenia caused by nephrotoxic chemotherapy: a single centre study

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Summary

Purpose: *To investigate the possible existence of increased nephrotoxicity caused by once-daily aminoglycosides in febrile neutropenic patients who were previously treated with cisplatin-based nephrotoxic chemotherapy.*

Methods: *Thirty-one patients with metastatic tumors received chemotherapy and, as a result, developed febrile neutropenia. Patients were stratified with regard to chemotherapy with cisplatin (n=15) or without cisplatin (n=16). Both groups received i.v. empiric antibiotic treatment which included combinations of once-daily aminoglycosides (amikacin vs. gentamicin) with beta-lactams.*

Results: *Increased nephrotoxicity due to administered aminoglycosides appeared significantly more frequently ($p<0.05$) in patients who received cisplatin-based chemotherapy. Increased nephrotoxicity differed significantly between various aminoglycosides regimens ($p<0.05$), being greater in the gentamicin group.*

Conclusion: *These results showed that cisplatin-based chemotherapy followed by a once-daily aminoglycosides regimen caused increased renal toxicity, which was more pronounced in patients treated with gentamicin vs. those treated with amikacin.*

Key words: aminoglycosides, cisplatin, febrile neutropenia, nephrotoxicity

Introduction

Chemotherapy-induced fever in cancer patients is closely linked to infection, especially in granulocytopenic patients. Since fever can be the only sign of infection in neutropenic patients, its appearance requires a series of diagnostic and therapeutic measures to be taken empirically, without the precise knowledge of the nature and cause of the infection [1]. The beneficial effect of aminoglycoside-containing combinations with beta-lactam is considered to be the standard empirical antimicrobial therapy for febrile neutropenia [2-4].

Despite their potential nephrotoxicity and ototoxicity and problems associated with aminoglycoside-resistant organisms, aminoglycoside antibiotics remain valuable and sometimes indispensable for the treatment of various infections and prophylaxis in special situations. Drug treatment is aimed to achieve a maximum therapeutic benefit while minimizing undesirable effects. The bactericidal efficacy of aminoglycosides is directly related to peak serum concentration (Cmax). Minimum serum concentration (Cmin) is related with toxicity. The pharmacokinetic monitoring (therapeutic drug monitoring) can improve the safety and efficacy of once-daily administration of aminoglycosides [5]. Therapeutic drug monitoring has been used in the assessment of toxicity of aminoglycosides by the TDx/ TDxFLx-assay which utilizes Fluorescence Polarization Immunoassay (FPIA) technology. TDx/ TDxFLx aminoglycoside assay is agent system for the quantitative measurement of aminoglycoside in the serum [6].

Cisplatin (cis-dichlorodiammineplatinum II) is a coordinate metal complex with significant antineoplastic activity and various adverse effects, including acute and chronic renal insufficiency and renal magnesium loss. Nephrotoxicity appears to be localized in the proximal convoluted tubules of the kidney [7]. The risk for these adverse effects is related to the dose and interval of cisplatin therapy and may be minimized by adequate hydration [8].

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Received 06-04-2009; Accepted 03-07-2009

The aim of this study was to investigate the possible existence of increased nephrotoxicity caused by once-daily administration of aminoglycosides in febrile neutropenic patients who were previously treated with nephrotoxic polychemotherapy containing cisplatin.

Methods

This prospective cohort study was conducted at the Department of Medical Oncology of the Institute for Oncology and Radiology of Serbia between July 1999 and December 2003. The eligibility criteria were: diagnosis of malignant disease; absolute neutrophil count (ANC) < 0.5×10^9/L at the onset or assumed to become < 0.5×10^9/L within one week after the onset of chemotherapy; fever (temperature >38° C) in the absence of a noticeable cause; no parenteral antibacterial drugs for at least 2 weeks before randomization; no known allergy to study drugs; normal initial creatinine levels (serum and clearance); normal liver function tests or within the following limits: ALT and AST<2.5×N, total bilirubin<1.5×N; patients who had understood the content of the investigation and had given their written informed consent for participation; and age over 18 years.

Cancer patients with febrile neutropenia (n=31) were enrolled; 14 received amikacin-based antibiotic regimen and 17 gentamicin-based antibiotic regimen. Characteristics of the study population are shown on Table 1. Patients were divided into two subgroups: patients who received cisplatin-containing regimen (n=15), and those who received chemotherapy without cisplatin (n=16; Figure 1). The two arms were balanced according to sex, age, performance status (PS) and presence of either advanced or metastatic disease. The majority of patients had satisfactory PS: 81% patients had ECOG

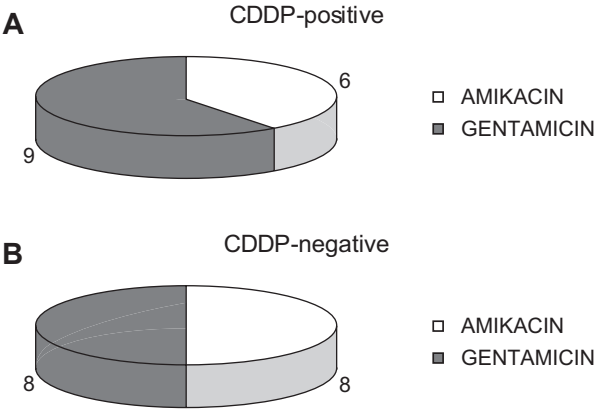

Figure 1. Number of patients who received amikacin vs. gentamicin in relation to chemotherapy regimen. CDDP-positive: chemotherapy containing cisplatin; CDDP-negative: chemotherapy without cisplatin.

Table 1. Characteristics of patients with febrile neutropenia

Characteristics	*CDDP⁺*		*CDDP⁻*	
	Amikacin n (%)	*Gentamicin n (%)*	*Amikacin n (%)*	*Gentamicin n (%)*
Febrile neutropenia	6 (40)	9 (60)	8 (50)	8 (50)
Mean age, years (range)	48 (32-64)		37 (21-53)	
Gender				
Male	3 (43)	5 (62.5)	6 (60)	3 (50)
Female	4 (57)	3 (36.5)	4 (40)	3 (50)
ECOG PS				
0-1	5 (83.4)	7 (77.8)	8 (80)	5 (83.3)
≥ 2	1 (16.6)	2 (22.2)	2 (20)	1 (16.7)
ANC				
$\leq 0.1\times10^9$	1 (14.3)	1 (12.5)	0 (0)	0 (0)
$< 0.5\times10^9$	6 (85.7)	7 (87.5)	6 (100)	10 (100)
Underlying disease				
Hematologic malignancy	1 (12.5)	2 (28.6)	5 (50)	2 (33.3)
Solid tumor	7 (87.5)	5 (71.4)	5 (50)	4 (66.7)
Total no. of metastatic sites				
0	1 (12.5)	1 (14.3)	2 (20)	0 (0)
1	7 (87.5)	5 (71.4)	8 (80)	5 (83.3)
≥ 2	0 (0)	1 (14.3)	0 (0)	1 (16.7)
Stage of disease				
Locally advanced	2 (28.6)	3 (37.5)	2 (33.3)	5 (55.6)
Metastatic	5 (71.4)	5 (62.5)	4 (66.7)	4 (44.4)

CDDP⁺: cisplatin-containing chemotherapy, CDDP⁻: chemotherapy without cisplatin, ECOG PS: Eastern Cooperative Oncology Group performance status, ANC: absolute neutrophil count

Table 2. Primary location of tumors and chemotherapy regimens

Primary location of tumors	*Number of patients (%)*	*Chemotherapy regimen*
Cancer of the head and neck	6 (19.35)	Cytosar 500/m^2, D1 5FU 800 mg/m^2, D1-D4 Cisplatin 100 mg/m^2, D1
Cancer of the breast	2 (6.45)	Docetaxel 100 mg/m^2, D1
Sarcomas of soft tissue and bone	13 (41.9)	
	2	1. Etoposide 60 mg/m^2, D1-D4 Carboplatin 40 mg/m^2, D1-D4
	5	2. Epirubicin 50 mg/m^2, D1-D3 Cisplatin 30 mg/m^2, D2-D5
	1	3. EVAIA Dactinomycin 0.5 mg/m^2, D1-D3 Ifosfamide 2 mg/m^2, D1-D3 Etoposide 150 mg/m^2, D1-D3 Vincristine 1.5 mg/m^2, D1
	5	4. HD-IPM Ifosfamide 1.7 mg/m^2, D1-D10
Non-Hodgkin's lymphoma	2 (6.45)	CHOP Cyclophosphamide 750 mg/m^2, D1 Doxorubicin 50 mg/m^2, D1 Vincristine 1.4 mg/m^2, D1 Prednisone 80 mg/m^2, D1-D5
Hodgkin's disease	4 (12.9)	EVAP Etoposide 100 mg/m^2, D1-D4 Vinblastine 6 mg/m^2, D1 Doxorubicin 50 mg/m^2, D3 Prednisone 50 mg/m^2, D1-D7
Cancer of the stomach	1 (3.22)	EAP Doxorubicin 40 mg/m^2, D1 Etoposide 300 mg/m^2, D1 Cisplatin 80 mg/m^2, D1
Cancer of the testis	1 (3.22)	TEP Paclitaxel 60 mg/m^2, D1, D8, D15 Etoposide 100 mg/m^2, D1-D5 Cisplatin 20 mg/m^2, D1-D5
Ovarian cancer		PC Cyclophosphamide 500 mg/ m^2, D1
	2 (6.45)	Cisplatin 75 mg/m^2, D2

D: days

PS 0-1 and 19% ECOG PS 2. No significant differences in duration and intensity of granulocytopenia were documented between the two patient groups with regard to chemotherapy regimen (cisplatin-containing vs. non cisplatin-containing regimen; p=0.48). In the group of febrile neutropenic patients who received chemotherapy containing cisplatin the average dose of cisplatin was 90 mg/m^2 (range 75-120). The median dose intensity was 95 mg/m^2 in the amikacin group and 100 mg/m^2 in the gentamicin group of patients and there was no significant difference between those groups.

Treatment plan

Patients with febrile neutropenia received one of the following regimens: gentamicin 4 mg/kg once-daily plus ceftriaxone administered once daily at a dose of 2 g/day; or amikacin 15 mg/kg once-daily plus ceftriaxone administered once daily at a dose of 2 g/day. Antibiotic therapy was administered until replacement with a different antibiotic because of failure, toxicity or superinfection, or resolution of granulocytopenia (however, not less than 5 days). For both groups, patients were divided into those who received chemotherapy containing cisplatin or those who received chemotherapy without cisplatin (Table 2).

Clinical and laboratory monitoring

In every patient complete medical history was taken and physical examination was carried out. The following investigations were performed prior to trial admission: complete blood count, full serum biochemistry and creatinine clearance and chest radiography. Complete microbiological analyses performed prior to initiation of antibiotic treatment included routine blood cultures (at

least 2 blood cultures at intervals of no less than 1 h), and urine cultures. Cultures of a particular site, as indicated by the clinical findings (sputum, throat, stool), and any other supposed site of infection were also performed.

Evaluation of nephrotoxicity

Nephrotoxicity was assessed using the following parameters: serum creatinine, creatinine clearance, and serum Mg^{2+} levels. Those parameters were graded according to Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) [9].

Therapeutic drug monitoring

Therapeutic drug monitoring has been performed by determining the serum levels of amikacin and gentamicin. These levels were determined prior to initiation of antibiotic treatment, 30 min and 4 h after the end of an antibiotic infusion, and in 3 successive days after the beginning of administration. A Cmax level of gentamicin (peak serum concentration 30 min and 4 h after the end of the antibiotic infusion) > 12 mg/l was considered as renal toxicity level. A Cmax level of amikacin (peak serum concentration 30 min and 4 h after the end of the antibiotic infusion) > 30 mg/l was considered as renal toxicity level. A Cmin level of gentamicin (preinfusion levels) > 2.0 mg/l was considered as renal toxicity level. A Cmin level of amikacin (preinfusion levels) > 8.0 mg/l was considered as renal toxicity level.

Statistical analyses

Statistical analyses were performed using two-tailed tests with an alpha level of $p<0.05$. Differences between categorical variables were tested with univariate x^2 test, *t*-test and Fisher's exact test. The x^2 test was used to estimate differences in response rates between different aminoglycosides. Data analysis was performed with SPSS, version 6.1 for Windows, R-plus and S-plus. Efficacy was analysed for the modified intent-to-treat population (all enrolled patients who fulfilled the inclusion criteria).

Results

There was no statistical difference in creatinine clearance between cisplatin and noncisplatin regimen's group (Fisher's exact test, p=1.000). There was significant difference in creatinine clearance between patients who received cisplatin-containing chemotherapy in the amikacin group and those who did not (Fisher's exact test, $p <0.001$). There was no significant difference in creatinine clearance between patients who received cisplatin-containing chemotherapy in the gentamicin group and those who did not (Unpaired t-test, p=0.874).

There was no statistical difference in serum Mg^{2+} levels between cisplatin and noncisplatin groups (Fisher's exact test, p=0.113). There was no significant difference in serum Mg^{2+} levels between patients who received cisplatin-containing chemotherapy in the amikacin group and those who did not (Unpaired t-test p=0.848). There was significant difference in serum Mg^{2+} levels between patients who received cisplatin-containing chemotherapy in the gentamicin group and those who did not receive cisplatin (Fisher's exact test, $p <0.005$). Analysis of serum Mg^{2+} levels by descriptive statistics showed increased nephrotoxicity by different aminoglycosides in the group of patients who had previously received chemotherapy containing cisplatin, predominantly in the gentamicin group (Figure 2).

Statistically significant difference was noted in Cmax 4 h between patients who received cisplatin vs.

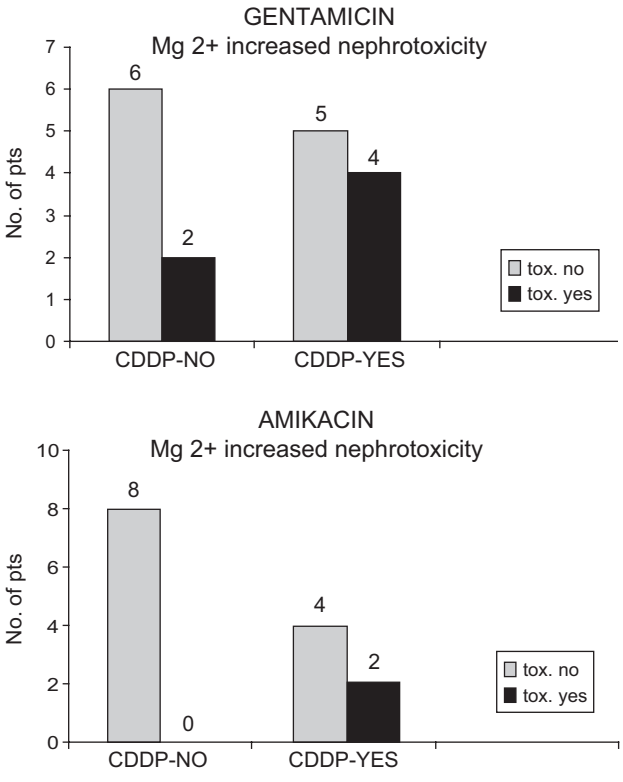

Figure 2. Increased nephrotoxicity by analysing Mg^{2+} depended on chemotherapy containing cisplatin and different aminoglycosides; amikacin vs. gentamicin.
CDDP-YES: chemotherapy containing cisplatin, CDDP-NO: chemotherapy without cisplatin, tox. no: not increased nephrotoxicity by aminoglycosides, tox. yes: increased nephrotoxicity by aminoglycosides, No. of patients: number of patients who developed nephrotoxicity.

those who did not (Fisher's exact test, p=0.028), while no significant difference in Cmax 4 h was seen between patients who received cisplatin-containing chemotherapy in the amikacin group vs. those who did not (Unpaired t-test, p=0.732). There was significant difference in Cmax 4 h between patients who received cisplatin-containing chemotherapy in the gentamicin group and those who did not (Fisher's exact test, p <0.001). Analysis of peak serum concentration (Cmax 4 h) by descriptive statistics showed that cumulative nephrotoxicity by different aminoglycosides occurred in the group of patients who had previously received chemotherapy containing cisplatin, predominantly in the group of patients who received gentamicin (Figure 3).

No statistical difference was observed in Cmin between patients who received cisplatin and noncisplatin chemotherapy (Fisher's exact test, p=0.597). Also no significant difference in Cmin was noted between patients who received cisplatin-containing chemotherapy and those who did not in the amikacin group (Unpaired t-test, p=0.535). In contrast, significant difference in Cmin between patients who received cisplatin-containing chemotherapy vs. those who did not was observed in the gentamicin group (Fisher's exact test, p <0.001).

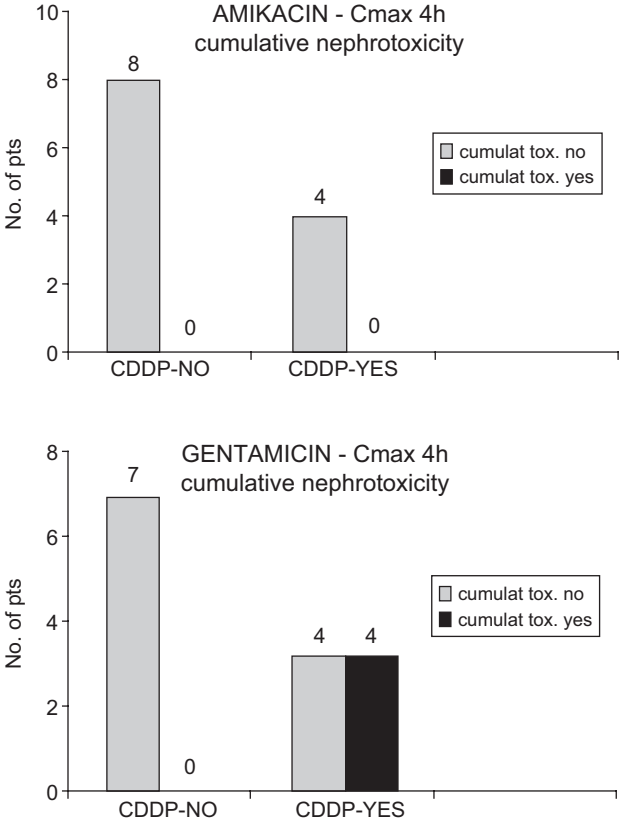

Figure 3. Cumulative nephrotoxicity analysed by Cmax 4h dependent on chemotherapy containing cisplatin and different aminoglycosides; amikacin vs. gentamicin.
CDDP-YES: chemotherapy containing cisplatin, CDDP-NO: chemotherapy without cisplatin, cumulat. tox. no: no cumulative nephrotoxicity by aminoglycosides, cumulat. tox. yes: cumulative nephrotoxicity by aminoglycosides, No. of pts: number of patients who developed nephrotoxicity. Cmax 4 h: Peak concentration of aminoglycoside obtained 4 h after the start of a 30-min infusion, determined by therapeutic serum drug level monitoring.

Discussion

When we planned this study, the combination of aminoglycoside and ceftriaxone was the standard empirical antibiotic therapy in our department. Our intent-to-treat analysis demonstrated that amikacin or gentamicin, both in combination with ceftriaxone were equally effective for the initial management of febrile cancer patients with severe neutropenia. Empirical antibiotic treatment of fever in cancer patients who become neutropenic as a result of previous chemotherapy has been found to diminish morbidity and mortality from infections [4]. In our study we administered a once-daily regimen of aminoglycosides, amikacin 15 mg/kg per day or gentamicin 4 mg/kg per day. The advantage of once-daily aminoglycoside therapy may be that routine monitoring of serum aminoglycoside concentration is not necessary, because a larger dose administered every 24 h will result in higher than usual peak concentration and lower than normal preinfusion levels and this would generate a pharmacoeconomic advantage for once-daily aminoglycoside administration [10,11]. Since therapy with aminoglycosides exerts a long post-antibiotic effect (2 or more hours), lower preinfusion levels should not jeopardize their clinical efficacy [11]. An EORTC trial has shown that a single daily dose of aminoglycoside and ceftriaxone is as effective and no more toxic than multiple daily dosing in the empirical treatment of infections in neutropenic cancer patients [12-14]. Aminoglycosides exhibit a narrow therapeutic index which makes their use hazardous, especially in patients with impaired renal function. Therefore, accurate monitoring of the serum level in such patients is mandatory [15,16].

In this study we analysed the cumulative nephrotoxicity as a result of aminoglycosides administration in febrile neutropenic patients in regard to previously administered chemotherapy. Statistically significant difference was obtained between cisplatin-containing and non-containing chemotherapy in aminoglycoside-dependent increased cumulative nephrotoxicity using the Cmax 4 h parameter. The cumulative nephrotoxicity was more pronounced and significant in the group of febrile neutropenic patients who were empirically treated with gentamicin vs. those who received amikacin. This is consistent with literature data that amikacin has the same spectrum of activity as gentamicin but is less susceptible to enzymatic inactivation. Therefore,

amikacin is valuable in managing infections caused by gram-negative bacilli resistant to gentamicin [13,17].

Cisplatin induces focal tubular necrosis through its renal toxicity, possibly by a direct injury to mechanisms of magnesium reabsorption in the ascending limb of the loop of Henle, although the morphological changes appear predominantly in the distal convoluted tubules and the collecting ducts [7]. This is comparable to magnesium loss following administration of gentamicin that has been described as an independent manifestation of renal toxicity [7,8]. The toxicity of aminoglycosides can be enhanced by the co-administration of other drugs and other nephrotoxic regimens can amplify the nephrotoxic potential of aminoglycosides [15,18]. These findings are in accordance with our results which showed increased nephrotoxicity of aminoglycosides by determining serum Mg^{2+} levels and revealed a significantly greater occurrence of nephrotoxicity in patients who received cisplatin, predominantly in the group of febrile neutropenic patients who were treated with gentamicin.

There are several limitations of our investigation that should be taken into consideration when interpreting the results, the main being that the number of patients included in our analysis was relatively small to allow safe conclusions regarding the effect and increased nephrotoxicity after the administration of aminoglycosides and cisplatin-containing chemotherapy. Despite this, we believe that this work adds useful information to the literature regarding the safety of once-daily aminoglycoside administration in the empirical antibiotic management of febrile neutropenic patients.

Our investigation of escalated nephrotoxicity by aminoglycosides in patients previously treated with cisplatin chemotherapy indicated a tendency for enhanced nephrotoxicity, which was more pronounced in the gentamicin group compared with the amikacin group. Thus, these data clearly indicate that an appropriate selection of antibiotics and a suitable method of their administration using combination regimens and once-daily aminoglycoside, particularly amikacin with cephalosporin, should allow significant cost reduction and improved outcomes in treating febrile episodes. These results may hopefully contribute to a better understanding of the increasingly important pharmacoeconomic aspects of antibiotic therapy in these difficult-to-manage patients with febrile neutropenia.

Acknowledgements

This study was supported by a grant from the Ministry of Science and Environmental Protection, Serbia (Project No. 145059).

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