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Changes of bone resorption marker (NTX) in chemotherapy plus zoledronic acid versus chemotherapy alone for nasopharyngeal cancer patients with bone metastases

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ABSTRACT

Background: Zoledronic acid (ZOL) is the only bisphosphonate with demonstrated efficacy for the prevention of skeletal-related events (SRE) in patients with bone metastases of diverse malignant tumours. A recent large, retrospective analysis reported that a reduction in N-telopeptide of type I collagen (NTX) provided a continuum of reduced SRE risk and survival benefit in patients with bone metastases. The present prospective, open-label, randomised, phase II trial sought to evaluate NTX changes after ZOL administration in nasopharyngeal cancer (NPC) patients with bone metastases (BM).

Methods: Newly diagnosed NPC patients ($n = 60$) with bone metastasis were randomised to the test group ($n = 30$), who received chemotherapy with cisplatin plus 5-fluorouracil (5-FU) (q3wks) and intravenous ZOL (4 mg, q4wks) for 3 months, or a control group ($n = 30$), who received cisplatin plus 5-FU alone. Urinary NTX was measured by ELISA at baseline and 1, 2 and 3 months after administration of ZOL.

Results: The median baseline NTX level was no different in both the test and control patients (75.4 and 94.6 nM bone collagen equivalent units/mM creatinine, respectively; $p = 0.370$). NTX decreased by 61.5% within 1 month in the test group, but only by 6.6% in the control group ($p < 0.01$). After 3 months, the test group reached a maximum reduction (−85.9%) as compared to the other time points and to the control group (−51.5%) ($p = 0.001$). More patients in the test group achieved normal NTX than that in the control group ($p = 0.042$).

Conclusions: ZOL administered with chemotherapy immediately and consistently reduced NTX levels for NPC patients with bone metastasis. Larger prospective randomised trial to confirm the efficacy of ZOL in NPC patients with bone metastases is pending.

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1. Introduction

Nasopharyngeal carcinoma (NPC) is endemic in China and the southeast Asian region where it has attained a peak incidence rate of around 20 per 100,000 person-years.[1] It poses a serious health problem in southern China. Distant metastasis is the major cause of mortality and treatment failure and overt distant metastasis has been detected in up to 11% of NPC patients at initial diagnosis.[2,3] The common sites of metastasis are the bone, lung and liver, and the skeleton is involved in 70–80% of distant metastasis.[2–4]

Bisphosphonates have emerged as an effective therapeutic option for the prevention of skeletal complications in patients with bone metastases of malignancies.[5,6] Third-generation bisphosphonates display the most potent antiresorptive efficacy and the third-generation amino-bisphosphonate, zoledronic acid (ZOL, ZOMETA; Novartis Pharma AG, Basel, Switzerland/Novartis Pharmaceuticals Corporation, East Hanover, NJ), has been approved in many countries worldwide for the treatment of bone metastases of malignancy.[7] However, its efficacy on the bone metastasis of NPC has not been investigated.

Metastatic bone disease is typically associated with a marked increase in bone resorption. N-telopeptide of type I collagen (NTX) is a bone resorption marker that is associated with the presence and extent of metastases, prognosis and response to treatment.[8–10] Other resorption markers such as deoxypyridinoline and pyridinoline have been investigated; however, their association with clinical characteristics appears to be inconsistent.[11–13] Recently, a large retrospective analysis reported that reductions in NTX levels are associated with a continuum of risk reduction of skeletal-related events (SRE) which include pathologic fracture, spinal cord compression, hypercalcemia of malignancy and radiotherapy or surgery to bone; and the association with survival benefit was seen regardless of baseline NTX levels.[14] Therefore, monitoring NTX changes may provide an insight into the response to therapy regardless of baseline NTX levels.[14] These observations support the use of NTX to assess the clinical progress of patients with metastatic bone disease. The aim of this prospective, open-label, randomised phase II trial was to compare the effects of cisplatin plus 5-fluorouracil (5-FU) with or without ZOL on the bone resorption marker NTX as an indirect evaluation of the antiresorptive efficacy of ZOL on NPC bone metastasis. Preliminary results of this study were presented in part at the Annual Meeting of the American Society of Clinical Oncology 2009.[15]

2. Patients and methods

2.1. Patients

Eligibility criteria consisted of (1) pathologically confirmed NPC; (2) at least one point of bone metastasis confirmed by enhanced computed tomography and X-ray/computed tomography/magnetic resonance imaging; (3) no radiotherapy or chemotherapy received after bone metastasis; (4) a life expectancy of more than 6 months; (5) an Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (6) adequate haematological and hepatic function; (7) serum creatinine <2.0 mg/dL (<1.5 times of the upper limit of the normal range); and (8) age $\geqslant$18 years. Patients with hyperostosis, additional malignancies, uncontrolled systemic diseases, previous treatment with any other biphosphonates, simultaneous participation in any other clinical trial, and pregnant and lactating women were excluded from the study. The study protocol was approved by the Research Ethics Committee of the Cancer Center of Sun Yat-Sen University and written informed consent was obtained from each patient. The protocol has been registered in http://register.clinicaltrials.gov as Registration ID NCT00697619.

2.2. Treatment plan

Patients newly diagnosed with NPC ($n = 60$) with bone metastasis were randomised to two groups. The test group of patients ($n = 30$) received chemotherapy using cisplatin (20 mg/m^2 IV, D1–5) plus 5-FU (500 mg/m^2 IV, D1–5) (CF regimen, q3wks) and intravenous ZOL (4 mg, q4wks, 3 times) with calcium (500 mg) and vitamin D (400–500 IU) tablet supplementation. The control group of patients ($n = 30$) received only the CF regimen. In cases where neutrophil count became $<1.5 \times 109$/L or platelet count became $<80 \times 109$/L, chemotherapy was withheld until normal values were re-established. In current study, the major end-point was the changes of NTX after 3 months' treatment of zoledronate, so the treatment duration of the clinical trial was 3 months. After that, the following treatment plan of the patients was worked out by their doctors.

2.3. Biochemical analysis

For NTX measurements, a midstream specimen of urine was obtained as a morning second-void sample at baseline and at time points of 1, 2 and 3 months after ZOL administration in all patients. Urine NTX was determined by enzyme-linked immunosorbent assay (ELISA; Osteomark; Ostex International, Seattle, WA) using a monoclonal antibody that recognises an epitope in the NTX crosslinking domain of type I collagen.[8] Urinary levels of NTX in bone collagen-equivalent units were expressed as a ratio to urine creatinine excretion. The reference range for NTX was 10–60 bone collagen equivalent units/mmol creatinine.

2.4. Statistical analysis

The difference of median change in the NTX/creatinine ratio after three months between the test and control groups was assumed to be about 25%. With 90% power, <5% type I error and an assumed expulsion rate of 20%, the protocol required a total of 60 patients (30 patients in each group). The median change in NTX/creatinine ratio was compared between the two groups. Statistical analyses were performed with the Mann–Whitney Test (two-tailed). Differences were considered to be statistically significant at $p < 0.05$.

3. Results

3.1. Patient characteristics

Between January 2006 and December 2008, a total of 60 patients were enrolled; 30 in each group. One patient in the control group was excluded because his urine samples were not available at final analysis (Fig. 1). The patients' characteristics are shown in Table 1. There were no apparent differences between the two groups in basic characteristics including gender, age and cycles of chemotherapy. However, the number of bone metastasis in the test group of patients was greater than that in the control group ($p < 0.05$). Median baseline NTX levels did not differ in the two groups.

3.2. NTX change in response to treatment

Levels of N-telopeptide, which have been shown to be an extremely sensitive measure of bone resorption when corrected for urinary creatinine levels, were measured in urine.[16] The median baseline NTX level was not different between the test and control groups (75.4 and 94.6 nM BCE/mM creatinine, respectively; $p = 0.370$). One month after treatment, median NTX levels had decreased in a statistically significant manner in the test group who received chemotherapy combined with ZOL versus the control group ($p < 0.001$). The data are summarised in Table 2.

The change from baseline NTX levels was calculated as [(baseline NTX – n-month NTX) ÷ baseline NTX] × 100, $n = 1$, 2, 3.[14] The maximum difference between treatment groups was observed in the first month of treatment with NTX levels decreasing by 61.5% in the test group and 6.6% in the control group ($p < 0.001$). The median NTX decrease percentage after 2 months treatment in the test group was 76.8% and in control group was 44.6%, $p < 0.01$. At the end of 3 months, the reduction in the test group was the highest (–85.9%) as compared to the values reported at other time points and as compared to the control group (–51.5%) ($p = 0.001$) (Fig. 2).

NTX levels <50 nM BCE/mM creatinine were characterised as normal.[17] At base line 39 (66.1%) of the 59 patients enrolled in our clinical trial had elevated NTX levels (NTX ≧ 50 nM BCE/mM creatinine), and 19 patients were in the test group, 20 in the control group. After three months' treatment, 17 patients (89.5%) in the test group achieved normal NTX level

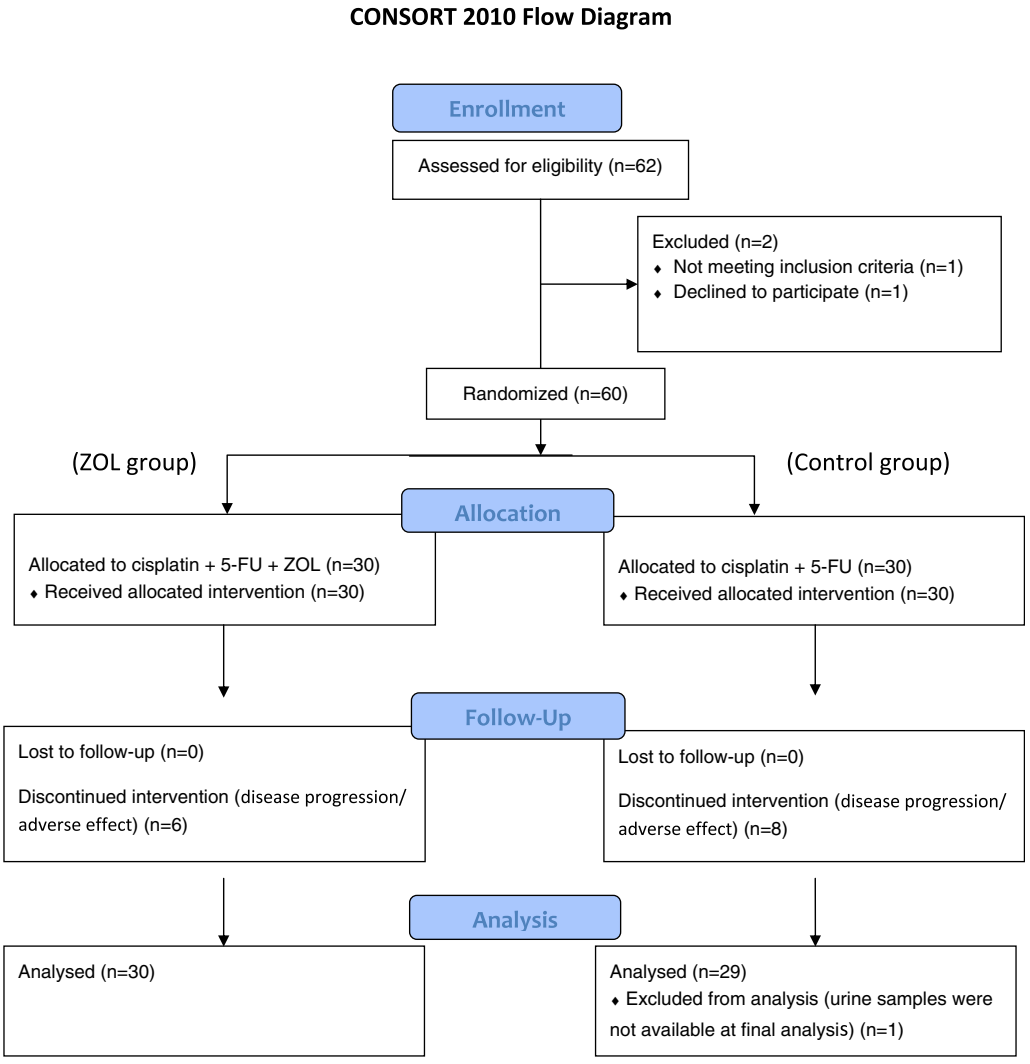

Fig. 1 – CONSORT diagram of the study. 5-FU, 5-fluorouracil; ZOL, zolendronic acid.

Table 1 – Baseline patient characteristics.

Parameter	Test group (n = 30)		Control group (n = 29)[a]	
	Number	%	Number	%
Gender				
Male	25	83.3	27	93.1
Female	5	16.7	2	6.9
Age, years (range)	47 (30–70)		45 (20–63)	
Number of patients completing 4 cycles of chemotherapy	24	80.0	22	75.8
Cancer Stage at first diagnosis				
I–II	2	6.7	2	6.9
III	13	43.3	8	27.6
IV	12	40.0	16	55.2
Other	3	10.0	3	10.3
Numbers of BM†				
1–2	6	20.0	16	55.2
⩾3	24	80.0	13	44.8
Median Baseline NTX levels‡ (BCE/mM creatinine)	75.4		94.6	

BM, bone metastases; NTX, N-terminal telopeptide of collagen.
[a] Sample unavailable so one patient was excluded from the study.
† $p < 0.05$, test group versus control group.
‡ $p = 0.370$, test group versus control group by the Mann–Whitney test.

Table 2 – Median NTX Levels.

NTX[a] (Median)	Baseline	Month 1	Month 2	Month 3
Test group	75.4	29.0	17.5	10.6
Control group	94.6	88.4	52.4	45.9
p-Value†	0.370	<0.001	0.006	0.002

NTX, N-terminal telopeptide of collagen .
[a] Levels expressed as nM BCE/mM creatinine.
† p-Value, Mann–Whitney test.

compared to only 11 patients in the control group (55.0%). The difference between two groups was statistically significant ($p = 0.042$).

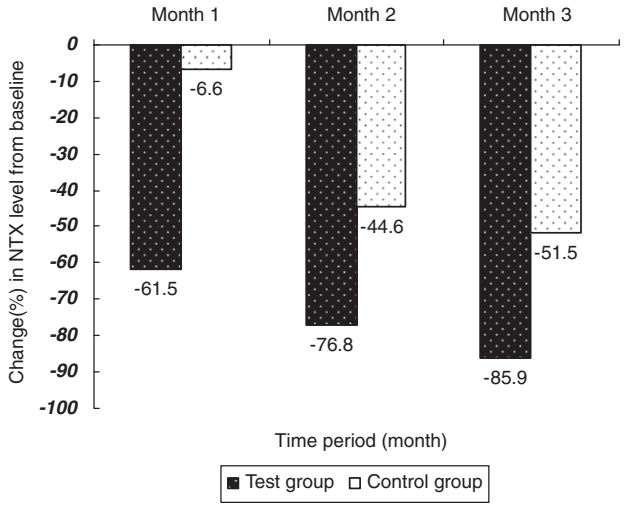

Fig. 2 – Change (%) in urine NTX levels from baseline at different time points for the duration of treatment.

3.3. *Clinical outcome*

With a median follow up of 17 months, the median survival time was 31 months (range 14–47) for all patients. The difference in median survival time between the two groups was not statistically significant, with a median of 20 months for the test group, compared with 30 months for the control group ($p = 0.27$). Eight patients (four in each group) developed SRE during the first 3 months of treatment. The most common type of SRE was radiation to the bone ($n = 7$), with the remaining SRE being spinal cord compression.

3.4. *Toxicity*

Chemotherapy-related toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3 and were listed in Table 3. The major Grade 3 or 4 toxicities were haematological toxicities such as leukopenia and neutropenia. The types and frequencies of complications were similar in the two groups. The most commonly reported adverse events caused by ZOL (bone pain, nausea, anemia, vomiting, constipation, dyspnea and fatigue) were no more serious in the test group than in the control group. No patient experienced serious side-effects such as severely decreased renal function or osteonecrosis of the jaw.

4. Discussion

Urinary NTX is a more valuable bone marker than alkaline phosphatase and C-telopeptide in assessing the antiresorptive effects of bisphosphonate therapy.[8] It is also a sensitive biomarker of bone resorption, and is reduced immediately and consistently after effective treatment. For patients with lung or prostate cancer with bone metastasis, NTX levels

Table 3 – Grade 3–4 toxicities.

Toxicity	Test group		Control group	
	No. of patients	%	No. of patients	%
Evaluable patients	30		29	
Leukopenia				
Grade 3	13	43.3	13	44.8
Grade 4	0	0	1	3.4
Neutropenia				
Grade 3	8	26.7	7	24.1
Grade 4	0	0	1	3.4
Thrombocytopenia				
Grade 3	2	6.7	1	3.4
Grade 4	0	0	0	0
Anemia				
Grade 3	4	13.3	5	17.2
Grade 4	0	0	0	0
Vomitting				
Grade 3	5	16.7	3	10.3
Grade 4	0	0	0	0
Diarrhea				
Grade 3	1	3.3	0	0
Grade 4	0	0	0	0
Stomatitis				
Grade 3	1	3.3	0	0
Grade 4	0	0	0	0
Renal toxicity				
Grade 3	0	0	0	0
Grade 4	0	0	0	0

are reduced by 1 month and remain significantly reduced throughout the treatment course in those treated with ZOL compared with placebo.[18,19]

The efficacy and safety of ZOL in patients with bone metastases secondary to NPC have not been evaluated comprehensively. A phase III clinical trial testing the efficacy of ZOL in solid tumours with bone metastases has enrolled only several patients with head and neck cancer, accounting for only 2–3% of each study group.[20] In our study, chemotherapy plus ZOL also reduced urinary NTX levels more effectively and quickly than chemotherapy alone in NPC patients with bone metastasis. In the test group, NTX levels exhibited a sharp decrease compared with the control group by the first month (61.5% versus 6.6%, respectively; $p < 0.001$). This decrease continued during the 3 month follow-up.

In a retrospective analysis, the percentage of patients with elevated baseline NTX levels was 58%, 61% and 43% in breast cancer (BC), hormone-refractory prostate cancer (HRPC), and advanced non small-cell lung cancer and other solid tumours (NSCLC/OST) with bone metastasis.[14] Within 3 months, zoledronic acid normalised NTX levels in 81%, 70% and 81% patients with BC, HRPC and NSCLC/OST, respectively.[14] For NPC patients in our trial, 39 (66.1%) had elevated baseline NTX level. After three months' treatment, 17 patients (89.5%) in the test group achieved normal NTX compared to only 11 patients in the control group (55.0%) ($p = 0.042$). Although, the cutoff point of normal NTX in the retrospective analysis (<64 nmol/mmol creatinine) was a little different from ours, the results still demonstrated that just like in other tumour types, Zol can also normalise NTX levels of NPC patients with bone metastasis.

The present phase II study was unable to detect any survival benefit in the test group of patients. This was because when the clinical trial was completed, most patients in the control group accepted treatment with ZOL in their subsequent therapy. Additionally, subsequent therapy for these patients usually included several different chemotherapy regimens, radiotherapy and biotherapy, which could not be balanced in the two groups. Moreover, at baseline, the number of metastases in the test group was more than that in the control group, which may have some effects on the patients' survival. For the same reasons, SRE proved not to be an ideal end-point to assess the efficacy of ZOL in NPC patients with bone metastasis.

ZOL was well-tolerated. Clinical adverse events such as nausea, anemia, vomiting, constipation, dyspnea and fatigue caused by ZOL were similar to those caused by chemotherapy, but were much less severe. As a result, these adverse events may effectively be ignored when combined with chemotherapy. There was no severely decreased renal function or osteonecrosis of the jaw in any patient.

In summary, this prospective, open-label, randomised phase II clinical trial demonstrates that chemotherapy plus ZOL reduces the urinary level of NTX, which is a sensitive biomarker of bone resorption, more quickly and effectively than chemotherapy alone in NPC patients with bone metastases. Given the phase II design of the trial, a larger prospective, randomised, phase III trial is needed to confirm the results.

Role of the funding source

The study sponsors had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Conflict of interest statement

None declared.

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