EUROPEAN JOURNAL OF CANCER 47 (2011) 848–853

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

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

Yuan-Yuan Zhao [a,d], *Cong Xue* [a,d], *Xue Hou* [c], *Hai Liao* [b], *Su Li* [b], *Hong-Yun Zhao* [b], *Yan Huang* [a], *Li-Kun Chen* [a], *Fei Xu* [a], *Jun-Ling Liu* [a], *Li Zhang* [a,b,*]

[a] *State Key Laboratory of Oncology in South China, Department of Medical Oncology, Cancer Centre, Sun Yat-Sen University, 651 Dong Feng Road East, Guangzhou 510060, PR China*

[b] *State Key Laboratory of Oncology in South China, National Anti-Cancer Drug Research Centre, Cancer Centre, Sun Yat-Sen University, 651 Dong Feng Road East, Guangzhou 510060, PR China*

[c] *Shanghai Lung Tumour Clinical Medical Center, Chest Hospital Affiliated to Shanghai Jiao Tong University, 241 West Huaihai Road, Shanghai, PR China*

ARTICLE INFO

Article history:
Received 14 September 2010
Received in revised form 6 December 2010
Accepted 7 December 2010
Available online 20 January 2011

Keywords:
Nasopharyngeal cancer
Bone metastases
Zoledronic acid
NTX

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.

* *Corresponding author at*: State Key Laboratory of Oncology in South China, Department of Medical Oncology, Cancer Centre, Sun Yat-Sen University, 651 Dong Feng Road East, Guangzhou 510060, PR China. Tel.: +86 20 8734 3458; fax: +86 20 8734 3392.
E-mail address: zhangli6@mail.sysu.edu.cn (L. Zhang).

[d] These authors contributed equally to this manuscript.

0959-8049/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2010.12.004

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 $p < 0.05$.