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ORIGINAL ARTICLE

Lobaplatin combined with docetaxel neoadjuvant chemotherapy followed by concurrent lobaplatin with intensity-modulated radiotherapy increases the survival of patients with high-risk lymph node positive nasopharyngeal carcinoma

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Summary

Purpose: *To evaluate the efficacy and safety of lobaplatin combined with docetaxel as neoadjuvant chemotherapy followed by concurrent lobaplatin with intensity-modulated radiotherapy (IMRT) for high-risk positive lymph node (N+) nasopharyngeal carcinoma (NPC).*

Methods: *This study enrolled 37 primary high-risk N+ NPC patients. The neoadjuvant chemotherapy program consisted of lobaplatin (30 mg/m², day 1) plus docetaxel (75 mg/m2, day 1) for two cycles, 3 weeks apart. Concurrently with IMRT, patients received a chemotherapy program of lobaplatin 50mg/ m². Cycle repetition was every 21 days. The IMRT doses were planning target volume (PTV) 68-72 Gy for gross disease in the nasopharynx, and 66-70 Gy for positive lymph nodes in 33 FRACTIONS. The doses for high risk and low risk region PTV were 59.4 Gy in 33 fractions and 50.4 Gy in 28 fractions.*

Results: *The median follow-up duration was 31 months (range 4-52). The 3-year overall survival (OS) was 74.3%. The 3-year distant metastasis-free survival (DMFS) was 67.4%. The 3-year locoregional relapse-free survival (LRFS) was 91.5%, and the 3-year progression-free survival (PFS) was 61.2%. The efficiency of short-term effects of neoadjuvant chemotherapy and chemoradiotherapy were 83.8% and 100.0%, respectively. Serious acute toxicities observed were neutropenia (97.3%), thrombocytopenia (83.8%) and anemia (81.1%).*

Conclusions: *In patients with high-risk N+ NPC, lobaplatin combined with docetaxel neoadjuvant chemotherapy followed by concurrent lobaplatin with IMRT yielded excellent short-term results with mild and tolerable toxicities.*

Key words: *docetaxel, high-risk nasopharyngeal carcinoma, intensity-modulated radiotherapy, lobaplatin, neoadjuvant chemotherapy*

Introduction

NPC is an Epstein-Barr virus-associated cancer with high incidence in Southeast Asia, and an annual incidence rate of 20-30/100,000 in China . Early stage NPC can be cured by radical radiotherapy. However, the range of the 5-year survival rates of stage III or IV NPC patients remain between 56 and 85% due to the high rate of local and distant treatment failure. High-risk factors for NPC distant metastasis include T4N2, N3 and at least a lymph node diameter > 4 cm in multiple lymph nodes. Lymph node staging is the most important prognostic factor affecting DMFS. Approximately 70% of newly diagnosed NPC patients present with cervical lymph node metasta-

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sis (N+) and the distant metastasis rate is significantly higher in advanced N stage patients. The current clinical challenge is reducing the rate of distant metastasis and improving the prognosis of NPC patients with distant metastasis.

IMRT offers advantages in terms of target coverage and sparing organs at risk (OAR) when compared to the frequently used conventional two-dimensional (2D-RT) and 3-dimensional conformal radiation (3D-RT) techniques. The adoption of IMRT has markedly improved the treatment outcome of NPC patients and increased the 5-year local control rate to more than 90%, while maintaining a distant metastasis rate of 15-25%.

Lobaplatin combined with docetaxel has achieved a high response rate in metastatic NPC and demonstrated good anti-tumor effects in preclinical studies of multiple solid tumors. This treatment modality has been increasingly applied in clinical practice because of its combined curative effect and acceptable toxicity in different cancers. Neoadjuvant chemotherapy has achieved improved locoregional control and event-free survival for NPC patients, but its efficacy regarding OS remains to be determined. Considering the demonstrated improvement in clinical outcomes for NPC patients offered by IMRT and neoadjuvant chemotherapy, we hypothesized that combined neoadjuvant chemotherapy and IMRT may increase the OS of NPC patients.

In the present study, we evaluated the clinical efficacy and toxicities of two cycles of lobaplatin combined with docetaxel followed by lobaplatin concurrent with IMRT in primary high-risk N+ NPC patients.

Methods

Ethical statement

This study was reviewed and approved by the Ethics Committee of The People's Hospital of Hainan Province, Haikou, China. Written informed consent was obtained from each patient.

Patients

Thirty-seven patients with high-risk N+ NPC were recruited in our hospital between November 2010 and May 2012 for this study. These patients had histologically confirmed non-keratinizing carcinoma without distant metastasis. Karnofsky performance scores were > 80. Clinical and laboratory examination methods included plasma EBV DNA test, nasopharynx and neck magnetic resonance imaging (MRI), endoscopy with histological confirmation of NPC, chest and abdominal CT and electroconvulsive therapy (ECT). All NPC patients were staged according to the 7th Edition of the American Joint Committee on Cancer (AJCC) TNM classification system. The histological diagnosis of each patient was graded according to the World Health Organization (WHO) 2003 classification for NPC. The clinical characteristics of the patients in the study are shown in Table 1.

Chemotherapy

The neoadjuvant chemotherapy program consisted of two cycles of lobaplatin (30 mg/m^2, day 1) plus docetaxel (75 mg/m^2, day 1), given 3 weeks apart . Concurrent with radiotherapy, patients received a chemotherapy program consisting of lobaplatin 50 mg/m^2, day 1. The cycle repetition was every 21 days. Throughout the whole course of chemotherapy, liver and renal function tests and routine blood and serum tests were performed.

IMRT

All patients were given IMRT synchronized with the third cycle of chemotherapy. Each patient was immobilized in supine position with a thermoplastic

Table 1. Clinical characteristics of NPC patients

Characteristics	*Patients, N*	*%*
Age (years)		
Median	44	
Range	26-65	
Sex		
Male	25	67.6
Female	12	32.4
T stage		
1	4	10.8
2	15	40.5
3	10	27.0
4	8	21.6
N stage		
1	7	18.9
2	16	43.2
3a	3	8.1
3b	11	29.7
Clinical stage		
II	5	13.5
III	10	27.0
IVa	8	21.6
IVb	14	37.8
EB DNA		
≥ 5.0E+2 copies/ml	33	89.2
< 5.0E+2 copies/ml	4	10.8

EB: Epstein-Barr virus

mask. A CT scan from the supraorbital margin to 3 cm below the clavicle was performed with a 3 mm slide thickness. IMRT was accomplished using nice coplanar beams. Outlined target area data were processed by the treatment planning system to prepare the radiotherapy plan and prescribed dose. The gross tumor volume (GTV) included the nasopharynx gross tumor volume (GTVnx) and positive neck lymph nodes (GTVnd). Except for skull bone destruction, these measures were sketched based on the regression after chemotherapy. High-risk clinical tumor volume (CTV1) included the entire nasopharyngeal mucosa, retropharyngeal lymph nodes, skull base, parapharyngeal space, pterygopalatine fossa, sphenoid sinus, posterior third of the nasal cavity and maxillary sinus. CTV1 encompassed GTVnx and GTVnd. Low-risk clinical tumor volume (CTV2) included tumors without associated lymph node metastasis in the cervical lymph drainage area. The lymph drainage area for the low-risk area included the lower neck and supraclavicular lymph nodes. The PTV was calculated based on each GTV and CTV, with an additional 3 mm margin to account for a potential positioning error of 3 mm. PTVs approaching the brain and spinal cord were reduced according to radiotherapy requirements. The prescribed doses were PTV 68-72 Gy for gross disease in the nasopharynx, and 66 - 70 Gy for positive lymph nodes in 33 fractions. The prescribed doses for high and low risk region PTVs were 59.4 Gy in 33 fractions and 50.4 Gy in 28 fractions, respectively. IMRT was delivered once daily (one fraction), with 5 fractions per week. The dose received by each OAR was no more than its tolerance limit, as defined by the International Commission on Radiation Units and Measurements (ICRU) 83.

Follow-up

Short-term effect of neoadjuvant chemotherapy: After two cycles of neoadjuvant chemotherapy, cervical lymph nodes were assessed by local CT. Short-term effect of chemoradiotherapy: three months after radiotherapy, cervical lymph node metastases regression was recorded by ultrasound. Each patient was scheduled for follow-up visits every 3 months. Each follow-up visit included a chest X-ray, abdominal ultrasound and endoscopy. MRI of the head and neck and ECT were performed every 6 months. Toxicities were observed and scored according to the Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG). Efficacy was determined using the Response Evaluation Criteria In Solid Tumors (RECIST) which were defined as follows: complete response (CR): visible lesions completely disappear over the course of one month; partial response (PR): tumor size is reduced by more than 50% in no less than four weeks; no change (NC): tumor size is reduced by less than 50% or increased by no more than 25%; progression of disease (PD): tumor size is increased by more than 25% or new lesions are formed. Total efficiency was calculated according to the following formula: total efficiency = (CR + PR) / total number of cases×100%.

Statistics

Data were analyzed using SPSS 21.0 (IBM Corp., Armonk, NY, USA) software. The Kaplan-Meier method was used to calculate OS, distant DMFS, LRFS and PFS. p values < 0.05 were considered statistically significant.

Results

Short-term effect of neoadjuvant chemotherapy

After neoadjuvant chemotherapy, one patient achieved CR (2.7%) and 30 (81.1%) patients PR. Thus, the total short-term efficiency of neoadjuvant chemotherapy was 83.8% (Table 2). MRI showed that lymph nodes with liquefaction necrosis subsided significantly slower than solid lymph nodes ($p<0.01$). Furthermore, fixed lymph nodes subsided more slowly than active lymph nodes when assessed by palpation ($p<0.05$).

Short-term effect of chemoradiotherapy

Three months after radiotherapy, total chemoradiotherapy efficiency was 100.0% with 33 CR and 4 PR (Table 2). For the 4 PR patients, ultrasound studies showed reduced blood supply in the lymph nodes which did not fully subside. Three were self-limiting within 6 months, while the remaining patient exhibited solidification changes during a long-term follow-up examination.

Adverse reactions

All 37 patients completed two courses of neoadjuvant chemotherapy and at least one cycle of concurrent chemoradiotherapy. Six cases were prolonged by cycle repetition or an interruption

Table 2. Treatment's clinical efficiency

Efficiency	*CR* *N (%)*	*PR* *N (%)*	*NC* *N (%)*	*PD* *N (%)*
Short-term effect of neoadjuvant chemotherapy	1 (2.7)	30 (81.1)	6 (16.2)	0 (0)
Short-term effect of chemoradiotherapy	33 (89.2)	4 (10.8)	0 (0)	0 (0)

For abbreviations see text

of chemotherapy due to thrombocytopenia or mucositis. The main adverse reactions were hematologic toxicity and mucositis. Patients exhibited a relatively low incidence of vasculitis. Acute toxicities experienced by patients are summarized in Table 3. Chronic toxicities were mainly grade I-II radiation-induced xerostomia (14 cases). There was a single case of radiation encephalopathy, 6 cases of hearing loss and three cases of neck skin fibrosis. No cases of radiation-induced cranial nerve damage or trismus were observed.

Patterns of failure

Patients were followed from 4 to 52 months, with a median follow-up duration of 31 months. The overall failure rate was 35.1% (13 patients; Table 4), including one local recurrence and one parotid lymph node metastasis. Distant metastasis was the main cause of failure and the most common metastasis site was bone. Eleven patients experienced distant metastases (29.7%). The median distant metastasis time was 10 months (range 2 – 31).

Survival

Kaplan-Meier analysis showed 3-year OS (Figure 1A), DMFS (Figure 1B), LRFS (Figure 1C) and PFS (Figure 1D) rates of 74.3, 67.4, 91.5 and 61.2%, respectively.

Discussion

In this study, we treated 37 primary high-risk N+ NPC patients with lobaplatin combined with docetaxel as neoadjuvant chemotherapy followed by lobaplatin concurrently with IMRT. Our results demonstrated that this combinatorial treatment strategy yielded excellent short-term results, with mild and tolerable toxicities. These results suggest that this strategy could be easily applied in clinical practice.

The majority of NPC cases diagnosed in Southeast Asia are classified as WHO undifferen-

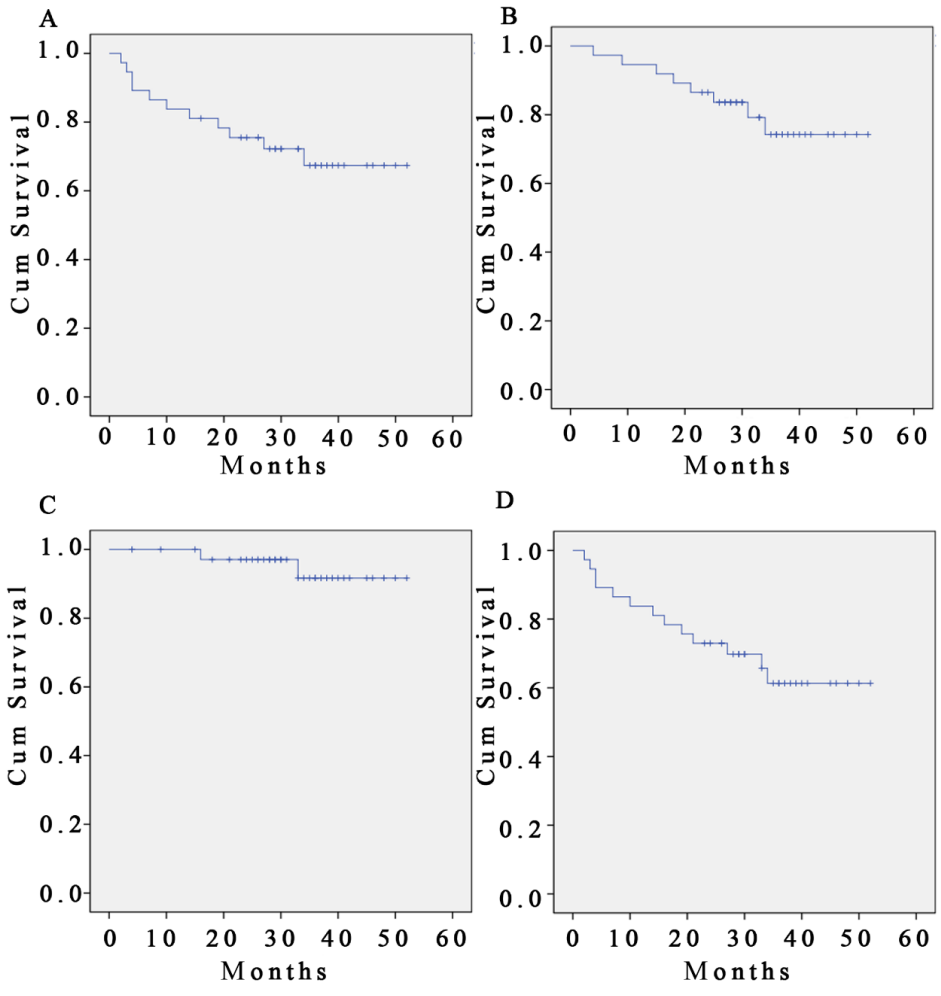

Figure 1. Kaplan-Meier analysis of nasopharyngeal carcinoma patients treated with chemoradiotherapy. (**A**) Overall survival. (**B**) Distant metastasis-free survival. (**C**) Locoregional relapse-free survival. (**D**) Progression-free survival.

Table 3. Treatment-related toxicities

Toxicities	*Grade*			
	I *N (%)*	*II* *N (%)*	*III* *N (%)*	*IV* *N (%)*
Dermatitis	26 (70.3)	5 (13.5)	1 (2.7)	0 (0)
Mucositis	14 (37.8)	18 (48.6)	4 (10.8)	0 (0.0)
Xerostomia	25 (67.6)	6 (16.2)	0 (0)	0 (0)
Neutropenia	9 (24.3)	14 (37.8)	13 (35.1)	0 (0)
Anemia	23 (62.2)	7 (18.9)	0 (0)	0 (0)
Thrombocytopenia	13 (35.1)	10 (27.0)	7 (18.9)	1 (2.7)
Nausea/vomiting	5 (13.5)	3 (8.1)	0 (0)	0 (0)
Liver dysfunction	4 (10.8)	1 (2.7)	0 (0)	0 (0)
Renal dysfunction	1 (2.7)	0 (0)	0 (0)	0 (0)
Fever	3 (8.1)	1 (2.7)	0 (0)	0 (0)
Neurotoxicity	1 (2.7)	0 (0)	0 (0)	0 (0)
Fatigue	7 (18.9)	0 (0)	0 (0)	0 (0)
Hypotension	4 (10.8)	0 (0)	0 (0)	0 (0)

Table 4. Sites of treatment failure

Sites	*Patients* *N*	*%*
Relapse	2	5.4
Local relapse	1	2.7
Parotid lymph node metastasis	1	2.7
Distant metastasis		
Bone	5	13.5
Lung	2	5.4
Liver	1	2.7
Multiple locations	3	8.1

tiated type III. Unlike the WHO type I NPC, commonly seen in Western counties, WHO type III NPC is relatively sensitive to chemoradiotherapy. Many studies have shown that the distant metastasis rate is significantly increased in advanced N stage patients, and that a high rate of distant metastases remains even following IMRT. These findings suggest that subclinical metastasis may already exist in distant organs prior to treatment in some patients. Tumor blood supply is beneficial for chemotherapeutic drugs, improving drug efficacy by allowing the drugs to exert a direct effect on the lesions. In addition to reducing tumor burden and hypoxic cells, chemotherapy can increase radiation sensitivity and kill micro-metastases, thereby reducing the rate of distant metastasis. In this study, we took advantage of these properties by applying induction chemotherapy before radiotherapy.

Docetaxel is a fat-soluble anticancer drug that exhibits efficient antitumor activity in head and neck tumors. It stabilizes microtubules and prevents the disassembly of microtubules during mitosis, thereby leading to catastrophic cell death. Lobaplatin is a third platinum generation anticancer drug that exhibits improved anticancer effects and reduced kidney toxicity and adverse gastrointestinal effects when compared with cisplatin. Platinum and its derivatives are DNA alkylating agents that cause cell death by inducing DNA damage and the collapse of DNA replication forks. In the present study, the total efficiency of combinatorial lobaplatin and docetaxel therapy was verified by the efficiency of short-term effects

of neoadjuvant chemotherapy and chemoradiotherapy of 83.8% and 100.0%, respectively. The rapid retreat of lymph nodes would cause target deformation. Therefore, CT location of IMRT after induction chemotherapy may be used to avoid high doses of skin exposure, thereby reducing the extent of radiation dermatitis and re-positioning of the planned target due to deformation. Furthermore, rapid tumor regression can increase patient confidence in and cooperation with the treating physician.

Direct comparisons between our single-arm study's results and other clinical trials is challenging because the collection of clinical data is very difficult. The toxicity of our therapeutic strategy was tolerable and, therefore, this strategy could be applied repeatedly. Hematologic toxicity, the most common moderate neutropenia, accounted for 97.3% of the observed toxicity, followed by 83.8% thrombocytopenia and 81.1% anemia. Platelet levels and anemia could be significantly improved after IL-11 and cobamamide treatment. For patients with fewer than 30×10^9 platelets, platelet transfusions could be given with a therapeutic dose of 12 U. Routine blood examination every three to four days during induction chemotherapy was used to detect and intervene as early as possible to avoid grade III-IV hematologic toxicity. During treatment, nausea, vomiting, liver and kidney dysfunction and other adverse reactions were mild. We found that distant metastasis remained the primary cause of treatment failure, probably due to insufficient chemotherapy cycles. Therefore, further exploration is still needed to find the optimal number of neoadjuvant chemotherapy cycles. However, increasing the number of neoadjuvant chemotherapy cycles will delay radiotherapy, and may decrease patient tolerance for concurrent chemoradiotherapy, increasing the occurrence of anemia as well as a number of other problems before radiotherapy. Targeted drugs in combination with neoadjuvant chemotherapy are a possible new direction that could solve these problems.

In order to ensure the smooth progress of concurrent chemoradiotherapy, we did not use two-drug combination chemotherapy. All patients were provided with vitamin b12 and recombinant bovine basic fibroblast growth factor (rb-bFGF) by inhalation once a day to prevent mucositis from the outset of radiotherapy. Moreover, various multivitamins and supplements were given, and nutritional intake was enhanced during treatment. Acute mucositis occurred 8 times, fewer than the 10 occurrences that would be expected during conventional radiotherapy. No grade IV mucositis and dermatitis were registered. The one-side 1b lymph node irradiation test protocol of our hospital is as follows: First, presence of 1b lymph node metastasis; second, presence of extensive 2a and 2b lymph node metastasis and integration; third, 2a area lymph nodes with diameter ≥ 3 cm. Using this system we can protect the submandibular gland and help alleviate long-term symptoms of dry mouth as much as possible. Simultaneously, to facilitate lymphatic reflux and reduce facial and submandibular edema after radiotherapy, we limited the lips and posterior cervical region to less than 25 Gy.

In summary, lobaplatin and docetaxel neoadjuvant chemotherapy plus lobaplatin concurrently with IMRT in high-risk N+ NPC patients was a feasible treatment strategy. The efficiency of short-term results was very satisfactory with generally tolerable side effects.

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References

1. Cao SM, Simons MJ, Qian CN. The prevalence and prevention of nasopharyngeal carcinoma in China. Chin J Cancer 2001;30:114-119.
2. Baujat B, Audry H, Bourhis J et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys 2006;64:47-56.
3. Lee AW. Overview of clinical trials for nasopharyngeal carcinoma (in the English literature). Chin J Cancer 2010;29:709-714.
4. Lin JC, Liang WM, Jan JS, Jiang RS, Lin AC. Another way to estimate outcome of advanced nasopharyngeal carcinoma--is concurrent chemoradiotherapy ade-

quate? Int J Radiat Oncol Biol Phys 2004;60:156-164.

5. Wang W, Feng M, Fan Z, Li J, Lang J. Clinical outcomes and prognostic factors of 695 nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. Biomed Res Int 2014:814948.
6. Wong FC, Ng AW, Lee VH et al. Whole-field simultaneous integrated-boost intensity-modulated radiotherapy for patients with nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2010;76:138-145.
7. Kam MK, Chau RM, Suen J, Choi PH, Teo PM. Intensity-modulated radiotherapy in nasopharyngeal carcinoma: dosimetric advantage over conventional plans and feasibility of dose escalation. Int J Radiat Oncol Biol Phys 2003;56:145-157.
8. Kristensen CA, Kjaer-Kristoffersen F, Sapru W, Berthelsen AK, Loft A, Specht L. Nasopharyngeal carcinoma. Treatment planning with IMRT and 3D conformal radiotherapy. Acta Oncol 2007;46:214-220.
9. Xia P, Fu KK, Wong GW, Akazawa C, Verhey LJ. Comparison of treatment plans involving intensity-modulated radiotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2000;48:329-337.
10. Long GX, Lin JW, Liu DB et al. Single-arm, multi-centre phase II study of lobaplatin combined with docetaxel for recurrent and metastatic nasopharyngeal carcinoma patients. Oral Oncol 2014;50:717-720.
11. Peng Y, Liu YE, Ren XC et al. A phase I clinical trial of dose escalation of lobaplatin in combination with fixed-dose docetaxel for the treatment of human solid tumours that had progressed following chemotherapy. Oncol Lett 2015;9:67-74.
12. Sun X, Lou LG, Sui DH, Wu XH. Preclinical activity of lobaplatin as a single agent and in combination with taxanes for ovarian carcinoma cells. Asian Pac J Cancer Prev 2014;15:9939-9943.
13. Xie CY, Xu YP, Jin W, Lou LG. Antitumor activity of lobaplatin alone or in combination with antitubulin agents in non-small-cell lung cancer. Anticancer Drugs 2012;23:698-705.
14. Xu L, Pan J, Wu J et al. Factors associated with overall survival in 1706 patients with nasopharyngeal carcinoma: significance of intensive neoadjuvant chemotherapy and radiation break. Radiother Oncol 2010;96:94-99.
15. Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet 2005;365:2041-2054.
16. Rottey S, Madani I, Deron P, Van Belle S. Modern treatment for nasopharyngeal carcinoma: current status and prospects. Curr Opin Oncol 2011;23:254-258.
17. Wu SY, Wu YH, Yang MW et al. Comparison of concurrent chemoradiotherapy versus neoadjuvant chemotherapy followed by radiation in patients with advanced nasopharyngeal carcinoma in endemic area: experience of 128 consecutive cases with 5 year follow-up. BMC Cancer 2014;14:787.
18. Lee AW, Lin JC, Ng WT. Current management of nasopharyngeal cancer. Semin Radiat Oncol 2012;22:233-244.
19. Wang J, Shi M, Hsia Y et al. Failure patterns and survival in patients with nasopharyngeal carcinoma treated with intensity modulated radiation in Northwest China: a pilot study. Radiat Oncol 2012;7:2-8.
20. He W, Zhang MG, Wang XJ et al. AURKA suppression induces DU145 apoptosis and sensitizes DU145 to docetaxel treatment. Am J Transl Res 2013;5:359-367.
21. Iida S, Shimada J, Sakagami H. Cytotoxicity induced by docetaxel in human oral squamous cell carcinoma cell lines. In Vivo 2013;27:321-332.
22. Shen G, Bian G, Yu H et al. Comparison between cisplatin plus vinorelbine and cisplatin plus docetaxel in the treatment of advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials. Mol Clin Oncol 2014;2:146-150.
23. McKeage MJ. Lobaplatin: a new antitumour platinum drug. Expert Opin Investig Drugs 2001;10:119-128.