

Original Article

Concurrent chemoradiotherapy with weekly docetaxel and cisplatin versus docetaxel and nedaplatin for locally advanced esophageal carcinoma

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Abstract: Here the research was designed to evaluate the safety and efficacy of weekly docetaxel and nedaplatin (DN) versus docetaxel and cisplatin (DP) when given concurrently with intensity-modulated radiotherapy (IMRT) in locally advanced esophageal carcinoma (EC). From January 2012 to January 2015, 71 patients were enrolled and randomly assigned to the DP group or the DN group. The two groups were both administered with IMRT at a single dose of 2 Gy/F per week for 5 days, 58-60 Gy totally. The DP regimen group was treated with 25 mg/m² docetaxel on day 1 and 25 mg/m² cisplatin (DDP) on day 2. In the DN regimen group, 25 mg/m² docetaxel was administered on day 1 and 25 mg/m² nedaplatin (NDP) on day 2. The results showed that there were no significant differences between the two groups in progression-free survival (PFS) (23.1% vs. 18.8%, P=0.541) or 2-year overall survival (OS) (41.4% vs. 37.5%, P=0.575). The median survival time of living patients was 18 months (95% CI, 11.131-24.869 months) in the DN group and 16 months in the DP group (95% CI, 10.456-21.544 months) (P>0.05). The main hematological toxicity was leukocytopenia, which affected 82.1% and 59.4% of the DN and DP groups, respectively (P=0.035). Non-hematological toxicities, such as gastrointestinal toxicity, occurred in 30.8% and 50.6% of the DN and DP groups, respectively (P=0.031). In conclusion, we initially found that IMRT concomitant with a DN regimen was a feasible alternative to DP, performed well, and was a beneficial treatment for EC.

Keywords: Esophageal squamous cell carcinoma, chemoradiotherapy, intensity-modulated radiotherapy, nedaplatin, locally advanced

Introduction

EC as a malignant tumor remains a “formidable foe” for physicians and patients, systemic therapies such as surgery, radiotherapy, chemotherapy and more are increasingly sophisticated, leading us closer to victory in constant exploration. In China, the most common histological subtype is squamous cell carcinoma, with over 480,000 new cases and 400,000 deaths annually [1, 2]. When the tumor is confined to the esophagus and the person’s physical condition is suitable for major surgery, surgical resection is the preferred treatment. However, the overall survival (OS) remains very poor even after radical surgery, and approximately 75% of treated patients succumb to loco-regional recurrence [3, 4]. Previous stud-

ies have shown that patients with advanced EC after radiotherapy (RT) alone have a 5-year survival rate of only 8-17% [5]. Therefore, radical synchronized chemoradiotherapy has become an important treatment measure for locally advanced esophageal cancer [6].

In the past few years, intensity-modulated radiotherapy (IMRT) have been all-around application and become one of the criteria for cancer radiotherapy. The implementation of IMRT allows the target volumes to achieve the formulate dose while reduce the dose of normal structures. Some trials have proved the superiority of concurrent chemoradiotherapy (CCRT) over RT alone in local EC patients [7]. Currently, chemotherapeutic drugs consist of DDP, NDP, 5-fluorouracil (5-FU), paclitaxel, docetaxel and

vindesine have been certified to treat EC in Japan. A number of recent studies have produced encouraging results using a regimen of DP concurrent with RT to treat EC patients [8-10], but the risk of gastrointestinal, hematological, and renal toxicity associated with DP-based regimens limits their use. Cis-diamminedichloroplatinum (nedaplatin, NDP), a second-generation platinum complex, is almost 10 times as soluble in water as cisplatin (DPP), exhibiting higher activity against certain solid tumors as well as lower nephrotoxicity and gastrointestinal toxicity [11-13]. Kobayashi H et al. [7] have found the cisplatin-resistant human leukemia cell lines was responsive to nedaplatin (1.0-fold) as parental cells, which had 10-fold resistance to DDP [14, 15] showing that NDP may be applied to patients who resistance to DDP. Recent studies have found that NDP-based chemotherapy has been effective to numerous cancers, involving non-small cell lung cancer, EC, uterine cervix, or head and neck [16] and demonstrated that patients with unresectable or advanced esophageal cancer achieved good results using DN as second-line combination chemotherapy [17]. Docetaxel, which proved single-agent activity in metastatic or recurrent EC has the function of stabilizing the microtubules as well as inhibiting mitosis, performed the different mechanism from NDP. Thus, we combined docetaxel and nedaplatin to achieve the purpose of satisfying anti-tumor effect with non-overlapping toxicological traits. Nevertheless, the regimen of docetaxel and nedaplatin is not commonly used at present and few reporters evaluating the efficacy and toxicity of CCRT, simultaneously, there have been no large studies comparing the weekly DP versus DN combined with IMRT for locally advanced esophageal cancer. Therefore, we conduct this study to investigate the efficacy and safety of the DN regimen and compared the two regimens.

Patients and methods

Patients

From January 2012 to January 2015 at Department of Radiation Oncology of the Qianfoshan Hospital, a total of 71 histologically diagnosed cases of ESCC patients included in this study. The patients were staged according to the 6th edition of the TNM staging system of the American Joint Committee on Cancer [18].

The agreement was approved by the Institutional Review Board which taking part.

All the enrolled patients met the following criteria: (1) histologically or pathologically confirmed locally advanced esophageal cancer that cannot undergo surgery or refuse to perform surgery; (2) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2; (3) previously untreated, had not received radiotherapy or chemotherapy before, no obviously related contraindications; (4) no other malignancy; (5) the use of the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [19] criteria to evaluate esophageal tumors that are measurable or assessable; (6) adequate bone marrow function (hemoglobin count greater than or equal to 9 g/dl, white blood cell level not less than 4,000/mm³, neutrophil count greater than or equal to 1,500/mm³, and platelet count greater than 100,000/mm³), hepatic function (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels no higher than the normal upper limit of 2.5-fold and a total bilirubin level less than or equal to 1.5 mg/dl), and renal function (serum creatinine level not higher than 1.5 mg/dl) [20]; (7) evaluation of cardiac function by electrocardiography and echocardiography within acceptable limits; (8) expected survival for three months or more; (9) willingness to provide written informed consent.

Exclusion criteria include: (1) accept other drug tests or acquiring anti-tumor therapy within 4 weeks; (2) other serious complications that made the treatment course cannot be completed; (3) pregnant or lactating women.

Treatment

Chemotherapy: All enrolled patients received chemoradiotherapy. The DP regimen group was treated with 25 mg/m² docetaxel on day 1 and 25 mg/m² DPP on day 2 starting the first week of RT. Irradiation was performed only for primary tumors and positive lymph nodes, and no lymph node selection was applied. In the DN regimen group, 25 mg/m² docetaxel was administered on day 1 and 25 mg/m² NDP on day 2 concurrently with IMRT. Docetaxel infusion took more than 1 hour, followed by NDP, which was also administered over 1 hour. All patients were given the appropriate drug for pretreatment 30 min before chemotherapy to prevent hypersensitivity reactions.

Table 1. Patient characteristics

Characteristic	DN (n=39)	DP (n=32)	X ²	P-value
Age			1.102	0.247
Median	60.6±5.1	61.8±4.3		
Range	45-70	52-70		
Sex			0.015	0.904
Male	30 (76.9)	25 (78.1)		
Female	9 (23.0)	7 (21.9)		
ECOG performance status			0.848	0.654
0	22 (56.4)	19 (59.4)		
1	16 (41.0)	13 (40.6)		
2	1 (2.6)	0 (0)		
Tumor location			0.869	0.648
Upper thorax	9 (23.1)	5 (15.6)		
Middle thorax	28 (71.8)	26 (81.3)		
Lower thorax	2 (5.1)	1 (3.1)		
Clinical stage			1.811	0.178
II	22 (56.4)	23 (71.9)		
III	17 (43.6)	9 (28.1)		

DN, refers to Docetaxel and nedaplatin; DP, refers to Docetaxel and cisplatin.

RT planning for IMRT: RT was performed using a 6 MV linear accelerator (TRUEBEAB VARIAN), which emits a photon beam from a linear accelerator or a microelectronic accelerator with a single dose of 2 Gy/F per week for 5 days, from the first day of the first cycle of chemotherapy. Individual patients received computed tomography (CT) scanning performed at 0.2-cm-thick slices. Gross tumor volume (GTV) included the primary tumor lesion and any nodal metastases visualized by CT and upper gastrointestinal endoscopy. Nodes with one or more of the following characteristics were considered involved: a short axis greater than or equal to 10 mm, lymphatic distribution of clusters, and the edge of the infiltration or lymph node center necrosis. The clinical target volume (CTV) consisted of a 3-D extension of 2-3 cm in the cephalad and caudal directions from the total target volume while expanding the edge 0.8-1.0 cm in the lateral and anteroposterior directions. The planning target volume was on the basis of the above-mentioned CTV, extending 2 cm on the longitudinal axis and the horizontal axis with a 0.5 cm margin [21]. The total dose applied to the spinal cord was not more than 45 Gy, and the dose constraints for lung tissue were a mean of 17 Gy and a V20 dose of 30%. The maximum dose tolerated by the esophagus did not exceed 58 Gy and 60 Gy for the circumference [22].

Assessment criteria

Response was assessed using RECIST criteria (Auperin A et al. 2010) as follows: (1) Complete response (CR) represented the total disappearance of all clinically detectable target cancer for more than 4 weeks; (2) Partial response (PR) indicated that the sum of the longest diameters of the original target lesion was reduced by at least 50% based on the total of each partial lesion's longest diameter; (3) The objective response rate (ORR) was defined as complete response (CR) and partial response (PR), (CR+PR). The duration from the date of initiation of chemotherapy to the last follow-up or progressive disease (PD) was considered PFS. OS time is the duration from chemotherapy initiation

until the patient died or the last follow-up. OS and PFS were analyzed using the Kaplan-Meier method, and the log-rank test was applied to evaluate differences in longer-survival patients. The follow-up period lasted for 10 years. Early toxicities referred to those occurring within three months after the completion of the chemotherapy. The severity of whole toxicities related to chemotherapy and radiation was assessed in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) grading system and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria [23, 24]. The toxicity symptoms that were evaluated during treatment included anemia, leukocytopenia, gastrointestinal problems, esophagitis and others. To evaluate the therapeutic effect and tumor recurrence, serum tumor markers were used as follows: carcinoembryonic antigen, squamous cell carcinoma-associated antigen [SCC], cytokeratin 19 fragment [CYFRA] and p53 antibody. The time of the assay was after the end of each month of treatment [25-27].

Statistical analysis

The statistical analysis was performed using SPSS for Windows, version 22.0 (SPSS, Chicago, IL, USA). The X² test or Fisher's exact test

Table 2. Toxicities

	DN group				Incidence	DP group				Incidence	P	P ^a
	I	II	III	IV		I	II	III	IV			
Anemia	10	2	1	0	28.2	8	2	5	2	53.1	0.033	0.029
Leukocytopenia	12	10	7	3	82.1	9	6	3	1	59.4	0.035	0.166
Neutropenia	13	11	4	2	76.9	9	5	2	1	53.1	0.035	0.690
Thrombopenia	9	3	5	2	48.7	6	2	0	0	25.0	0.041	0.034
Gastrointestinal	6	4	2	0	30.8	7	4	5	2	56.3	0.031	0.035
Esophagitis	14	12	1	0	69.2	12	8	2	1	71.9	0.808	0.216
Pneumonitis	7	2	1	0	25.6	6	2	1	1	31.3	0.601	0.442

P^a-values were calculated using the chi-squared test to compare grade 3-4 toxicities between the DP and DN patient groups.

Table 3. The responses to treatment

Response	Status	DN (n=39)	DP (n=32)	X ²	P-value
PFS (SD)	N	28 (71.8)	24 (75)	0.092	0.761
	Y	11 (28.2)	8 (25)		
PFS (PD)	N	37 (94.9)	31 (96.9)	0.174	0.676
	Y	2 (5.1)	1 (3.1)		
RR (CR)	N	29 (74.4)	26 (81.3)	0.478	0.489
	Y	10 (25.6)	6 (18.8)		
RR (PR)	N	12 (30.8)	13 (40.6)	0.748	0.387
	Y	27 (69.2)	19 (59.4)		

was applied to calculate statistical significance between categorical variables, and the association between the two sets of data were assessed by Pearson correlation analysis. The Commonly used toxicity criteria (version 3.0) were used to assess graded toxicity. Overall survival rate was calculated from the initial time of therapy making the use of Kaplan-Meier method, and the log-rank test was used to evaluate the differences among the survival curves. All P-values were two-tailed, and P<0.05 represented a statistically significant difference.

Follow-up

All enrolled patients were followed up every three months for the first three years of treatment and every six months thereafter. The relevant auxiliary examinations included physical examinations, complete blood count, serum chemistry, chest CT, and barium esophagography.

Results

Patients characteristics

Between January 2012 and January 2015, 137 ESCC patients participated in this study. We excluded 48 patients (35%) who accepted chemotherapy regimens other than DP or DN or who used other anti-cancer agents, as well as the one who refuse to participate in the study. In addition, we excluded 18 (13.1%) patients who could not finish the entire chemotherapy period. The remaining 71 patients were enrolled in this study. The cohort's demographic and clinical characteristics are listed in **Table 1**. Of the 71 patients in the cohort, the DN regimen was performed in 54.9% (n=39) of patients, whereas the DP regimen was used concurrently in 45.1% (n=32) of patients. Forty-five patients were stage II, and 26 patients were stage III. Patients in the trial both showed a tolerable ECOG performance status for treatment. All the enrolled patients had comparable characteristics, and there were no significant differences in age (p=0.247), sex (p=0.904), disease stage (p=0.178) or other characteristics (P>0.05).

Treatment delivery

All 71 patients received 4-6 weeks of DP or DN treatment. RT was given at a dose of 2 Gy/F, 5 days per week, DT58-60 Gy.

Toxicity

In the treatment period, hematological toxicity was evaluated every week. Common adverse reactions are listed in **Table 2**. Among the hematologic toxicities associated with treat-

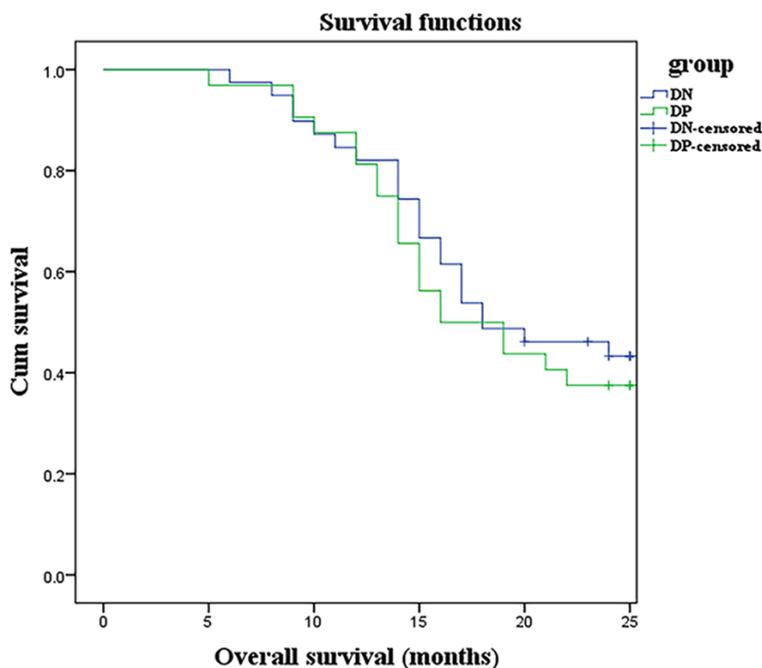


Figure 1. Kaplan-Meier analysis of overall survival (OS) times among patients treated with DN or DP regimen. MST, median survival time; DP, cisplatin; DN, nedaplatin.

ment, the most common was leukocytopenia. Six patients in the DN group experienced grade 3/4 neutropenia, whereas it affected three patients in the DP group (15.4% vs. 9.4%, $P=0.690$). Thrombopenia occurred in 48.7% and 25.0% of the DN and DP groups, respectively ($P=0.041$). Non-hematological toxicities, for instance, gastrointestinal toxicity, esophagitis, and radiation pneumonia, observed in this study are also listed in **Table 2**. Two and seven patients experienced grade 3-4 gastrointestinal toxicity in the DN and DP groups, respectively (5.1% vs. 21.9%, $P=0.035$). Gastrointestinal toxicity was more common in the DP group (18/32 vs. 12/39, $P=0.031$). Likewise, grade 3-4 esophagitis and radiation pneumonia had no significant differences between the DN and DP groups (1/39 vs. 3/32 and 1/39 vs. 2/32, respectively, $P>0.05$).

Tumor responses

Table 3 shows the responses to treatment. As shown, the overall tumor response rate was 87.3% (78.1-94.9%), and the median follow-up time was 29.0 months (range, 3-58 months). In the DN group, the median survival time (MST) was 18 months, and in the DP group it was 16 months ($P>0.05$). There were no significant dif-

ferences in 2-year OS (41.4% vs. 37.5%, $P=0.575$) or PFS (23.1% vs. 18.8%, $\chi^2=0.427$, $P=0.541$) between the two groups (**Figures 1, 2**). Among the 71 patients, 16 cases of CRs and 46 cases of PRs were confirmed. By the end of the first year, 35 patients had died: 21 cases because of disease progression, 12 cases from other complications, and 2 cases from sudden death.

Discussion

Esophageal cancer is considered to be one of the most common malignancies among people in China. Although the standard treatment for esophageal cancer is surgical excision, unfortunately, most patients with EC are found at the advanced stage due to a

variety of factors, missing the opportunity of surgery. For patients without surgical indications, radiotherapy alone or concurrent radiotherapy and chemotherapy is preferred to be a possible cure.

Radiotherapy is one of the main treatments for esophageal cancer, especially for locally advanced patients who are unable to undergo surgery or have contraindications to surgery. In some countries have recommended concurrent chemotherapy with radiotherapy as a standard treatment for locally advanced EC. In addition, there were three other prospective studies have shown that radiotherapy combined with chemotherapy showed radio-sensitization effects that can improve overall survival and enhance local control rate compared with radiotherapy alone [28]. As mentioned earlier in this article, studies have shown that a number of recent studies have produced encouraging results using a regimen of DP concurrent with RT to treat EC patients. As well, recent trails have proved that the combination-chemotherapy regimen of nedaplatin and docetaxel for refractory EC patients obtained good results [29-32]. NDP, as a derivative of DPP, has identical amine carrier ligands, but its leaving group of glycolate binds to platinum ions as a biden-

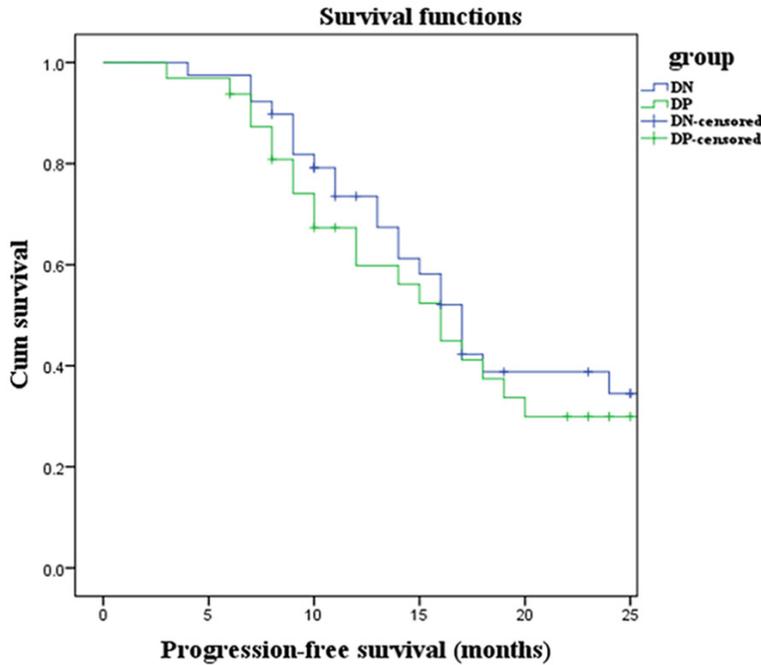


Figure 2. Kaplan-Meier curves of progression-free survival (PFS) times among patients treated with DN or DP regimen.

tate ligand to form a five-ring structure, resulting in differences from DPP, so we can infer that it may show relatively low toxicity (e.g., gastrointestinal toxicity, neurotoxicity, and nephrotoxicity) compared to DPP. Moreover, NDP does not require renal hydration and has high bioavailability [33]. However, there was a lack of analysis comparing the combination of NDP with the combined-modality of DDP on EC patients. Therefore, our study truly fills the gap above-mentioned and first found that although there is no significant benefit survival of DN regimen-synchronized IMRT for local advanced esophageal cancer compared with DP, with similar efficacy in OS and PFS between the two groups, what we delighted is that more patients in the DN group completed the full courses of CCRT, mainly because of the lower risk of anemia and gastrointestinal toxicities.

This study found that patients receiving DN did not exhibit significantly better OS or PFS than patients receiving DP. In total, 18 patients died within 1 year, and 10 patients survived for over 5 years without disease recurrence. The 1-year OS, 2-year OS and PFS rates were 51.2%, 41.4% and 23.1%, respectively, in the DN group and 46.9%, 37.5% and 18.8%, respectively, in the DP group ($P > 0.05$). During the treatment period, grade 3/4 hematological

and non-hematological toxicity was reviewed, with 2.6% and 21.9% of the DN group and DP groups, respectively, experiencing anemia ($P = 0.029$) and 5.1% and 21.9%, respectively, experiencing gastrointestinal side effects ($P = 0.035$). One case of grade 3-4 radiation pneumonitis occurred in the DN group, whereas 6.3% of the DP group experienced grade 3-4 events. At the same time, we observed a high incidence of grade 1-2 esophagitis in both groups. The treatment results are comparable to those of other studies. In a recently published study, Fei Zhang et al. [34] examined the safety and efficacy of these two regimens in the treatment of metastasis/relapses and advanced ESCC

using a systematic review and meta-analysis. Their study included 598 diagnosed patients who were enrolled in the analysis and received DPP-based or NDP-based regimens. The results showed that although the NDP-based regimen had no significant advantages in OS or ORR compared to DPP-based regimens, it had less toxicity and better tolerance, especially for patients susceptible to gastrointestinal side effects and with poor renal function. In a study in Japan, Akiko Kuwahara et al. [35] replaced DPP in the classic 5-FU/DPP-based CRT treatment for ESCC instead of NDP, and no significant difference was found in clinical outcome, i.e., the toxicities and CR rate in the NDP-based group were similar to those in the DPP-based group. Yamashita et al. [36] also investigated NDP in the treatment of metastatic or locally advanced EC and found that the OS, PFS and some hematological toxicities had no significant difference from DPP.

Additional factors should also be considered. Previous studies have shown that in dose determination factors, an esophageal volume dose of 45-50 Gy or more is a risk factor for developing esophagitis [37, 38]. It has been previously shown that the IFI technique delivers chemotherapy with a full dose, thus limiting the dose reduction or delay. Moreover, CRT

trials with full-dose chemotherapy during radiation have yielded satisfying results [39, 40]. In this study, the risk of hematologic toxicity was slightly higher for patients who received concurrent DP. Additionally, the incidence of gastrointestinal toxicity, esophagitis and pneumonitis was somewhat lower in the DN group. Hence, DN concurrent with radiotherapy is a relatively safe treatment for EC patients to choose.

Currently, some targeted drugs have been developed for EC treatment. One study identified LSD1 as a potential therapeutic target for ESCC and reported that the compound LPE-1 might lead to further anti-ESCC drug discovery [41]. However, the use of targeted drug methods is still limited compared to the CCRT mentioned in this article. For one thing, initially, patients need to bear the higher cost when using targeted drugs compared to traditional chemotherapy. Furthermore, some target agents like EGFR, HER2, c-MET, PI3K/Akt/mTOR are being currently assessed in clinical trials, but most of the results disappointing. A trial showed that, Gefitinib did not improve OS in EC patients that progressed on chemotherapy [42]. One study found that the regimen of lapatinib and chemotherapy was no significant improve the overall survival, just increased response rate in patients compared to chemotherapy alone [43, 44].

New drugs are being developed, and their roles in new regimens should be considered. Of course, the sample size of this study was relatively small, and the retrospective, single-institution design and lack of a follow-up period represent several inherent limitations. Differences in radiotherapy techniques should also be taken into account. Moreover, all the patients had a pathological type of phosphorus, so the results might be difficult to extrapolate to esophageal adenocarcinoma patients. Finally, it is necessary to conduct clinical trials, including pharmacogenomics analyses, in different racial groups; our study was performed in a Chinese population, which is pharmacologically different from Western populations, that will inevitably show different reactions and adverse events.

Conclusion

DN in combination with RT offers another treatment alternative for advanced or recurrent EC

with tolerable toxicity. The analysis indicated that the OS and PFS did not differ significantly between the DP and DN groups, but the DN regimen had fewer side effects than DP. More research is required to further clarify the mechanism of sensitivity to concurrent radiotherapy with weekly chemotherapy and to identify specific biological markers that predict drug efficacy.

Acknowledgements

We note that all patients who participated in this study provided written informed consents in accordance with the Declaration of Helsinki and consent for the publication.

Written informed consent was obtained from all patients. This study was approved by the Board and Ethical Committee of the Qianfoshan Hospital.

Disclosure of conflict of interest

None.

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References

- [1] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61: 69-90.
- [2] Rice TW, Rusch VW, Apperson-Hansen C, Allen MS, Chen LQ, Hunter JG, Kesler KA, Law S, Lerut TE, Reed CE, Salo JA, Scott WJ, Swisher SG, Watson TJ and Blackstone EH. Worldwide esophageal cancer collaboration. *Dis Esophagus* 2009; 22: 1-8.
- [3] Nakagawa S, Kanda T, Kosugi S, Ohashi M, Suzuki T and Hatakeyama K. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. *J Am Coll Surg* 2004; 198: 205-211.
- [4] Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C and Wilke H. Chemoradiation with and without surgery in patients with locally advanced squa-

- mous cell carcinoma of the esophagus. *J Clin Oncol* 2005; 23: 2310-2317.
- [5] Yeh AM, Mendenhall WM, Morris CG, Zlotecki RA, Desnoyers RJ and Vogel SB. Factors predictive of survival for esophageal carcinoma treated with preoperative radiotherapy with or without chemotherapy followed by surgery. *J Surg Oncol* 2003; 83: 14-23.
- [6] Stahl M, Budach W, Meyer HJ, Cervantes A; ESMO Guidelines Working Group. Esophageal cancer: clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; 21 Suppl 5: v46-49.
- [7] Jingu K, Matsushita H, Takeda K, Umezawa R, Takahashi C, Sugawara T, Kubozono M, Abe K, Tanabe T, Shirata Y, Yamamoto T, Ishikawa Y and Nemoto K. Long-term results of radiotherapy combined with nedaplatin and 5-fluorouracil for postoperative loco-regional recurrent esophageal cancer:update on a phase II study. *BMC Cancer* 2012; 12: 542-547.
- [8] Day FL, Leong T, Ngan S, Thomas R, Jefford M, Zalcborg JR, Rischin D, McKendrick J, Milner AD, Di Iulio J, Matera A and Michael M. Phase I trial of docetaxel, cisplatin and concurrent radical radiotherapy in locally advanced oesophageal cancer. *Br J Cancer* 2011; 104: 265-271.
- [9] Li QQ, Liu MZ, Hu YH, Liu H, He ZY and Lin HX. Definitive concomitant chemoradiotherapy with docetaxel and cisplatin in squamous esophageal carcinoma. *Dis Esophagus* 2010; 23: 253-259.
- [10] Ma HB, Di ZL, Wen J, Ke Y, Sun X and Ren J. Prospective, open, multicentre phase I/II trial to assess safety and efficacy of neoadjuvant radiochemotherapy with docetaxel and cisplatin for esophageal carcinoma. *Jpn J Clin Oncol* 2015; 45: 169-175.
- [11] Yamada H, Maki H, Takeda Y and Orita S. Evaluation of combined nedaplatin and docetaxel therapy for human head and neck cancer in vivo. *Anticancer Res* 2006; 26: 989-994.
- [12] Liu Y, Yu S, Liu S, Cao H, Ma R, Wu J and Feng J. Comparison of nedaplatin-based versus cisplatin-based chemotherapy for advanced non-small cell lung cancer among east asian populations: a meta-analysis. *Sci Rep* 2015; 5: 10516.
- [13] Zhang C, Li YL, Weng X, Li LY, Zhou MX, Zhang DY, Lin NM. Nedaplatin enhanced apoptotic effects of ABT-737 in human cancer cells via Mcl-1 inhibition. *Oncol Lett* 2016; 12: 4195-4202.
- [14] Kobayashi H, Takemura Y, Miyachi H and Oga-wa T. Antitumor activities of new platinum compounds, DWA2114R, NK121 and 254-S, against human leukemia cells sensitive or resistant to cisplatin. *Invest New Drugs* 1991; 9: 313-319.
- [15] Nakajima Y, Suzuki T, Haruki S, Ogiya K, Kawada K, Nishikage T, Nagai K and Kawano T. A pilot trial of docetaxel and nedaplatin in cisplatin-pretreated relapsed or refractory esophageal squamous cell cancer. *Hepatogastroenterology* 2008; 55: 1631-1635.
- [16] Shimada M, Itamochi H and Kigawa J. Nedaplatin: a cisplatin derivative in cancer chemotherapy. *Cancer Manag Res* 2013; 5: 67-76.
- [17] Gold PJ, Goldman B, Iqbal S, Leichman LP, Zhang W, Lenz HJ and Blanke CD. Cetuximab as Second-line therapy in patients with metastatic esophageal adenocarcinoma: a phase II southwest oncology group study (S0415). *J Thorac Oncol* 2010; 5: 1472-1476.
- [18] Nomura M, Shitara K, Kodaira T, Hatooka S, Mizota A, Kondoh C, Yokota T, Takahari D, Ura T, Muro K. Prognostic impact of the 6th and 7th American Joint Committee on Cancer TNM staging systems on esophageal cancer patients treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2012; 82: 946-952.
- [19] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228-247.
- [20] Kanekiyo S, Takeda S, Nakajima M, Nishiyama M, Kitahara M, Shindou Y, Michihisa I, Abe T, Yoshino S, Hazama S, Nagano H. Efficacy and safety of biweekly docetaxel in combination with nedaplatin as second-line chemotherapy for unresectable or recurrent esophageal cancer. *Anticancer Res* 2016; 36: 1923-1927.
- [21] Liu H, Lu L, Zhu Q, Hao Y, Mo Y, Liu M, Hu Y, Cui N and Rong T. Cervical nodal metastases of unresectable thoracic esophageal squamous cell carcinoma: characteristics of long-term survivors after concurrent chemoradiotherapy. *Radiother Oncol* 2011; 99: 181-186.
- [22] Poudenx M, Bondiau PY, Chamorey E, Venissac N, Otto J, Pourel N, Castelnau O, Tessier E, De Surmont Salasc B, Berdah JF, Pop D, Michel C and Mouroux J. Cisplatin-docetaxel induction plus concurrent 3-D conformal radiotherapy and weekly chemotherapy for locally advanced non-small cell lung cancer patients: a phase II trial. *Oncology* 2012; 83: 321-328.
- [23] Cox JD, Stetz J and Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; 31: 1341-1346.
- [24] Common terminology criteria for adverse events v3.0 (CTCAE). 2006.
- [25] Shimada H, Nabeya Y, Okazumi S, Matsubara H, Shiratori T, Gunji Y, Kobayashi S, Hayashi H and Ochiai T. Prediction of survival with squa-

- mous cell carcinoma antigen in patients with resectable esophageal squamous cell carcinoma. *Surgery* 2003; 133: 486-494.
- [26] Takahashi K, Miyashita M, Nomura T, Makino H, Futami R, Kashiwabara M, Katsuta M and Tajiri T. Serum p53 antibody as a predictor of early recurrence in patients with postoperative esophageal squamous cell carcinoma. *Dis Esophagus* 2007; 20: 117-122.
- [27] Wakatsuki M, Suzuki Y, Nakamoto S, Ohno T, Ishikawa H, Kiyohara H, Kiyozuka M, Shirai K, Nakayama Y and Nakano T. Clinical usefulness of CYFRA 21-1 for esophageal squamous cell carcinoma in radiation therapy. *J Gastroenterol Hepatol* 2007; 22: 715-719.
- [28] Sause WT, Scott C, Taylor S, Johnson D, Livingston R, Komaki R, Emami B, Curran WJ, Byhardt RW, Turrisi AT, et al. Radiation therapy oncology group (RTOG)88-08 and eastern cooperative oncology group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* 1995; 87: 198-205.
- [29] Fujita Y, Hiramatsu M, Kawai M, Sumiyoshi K, Nishimura H and Tanigawa N. Evaluation of combined docetaxel and nedaplatin chemotherapy for recurrent esophageal cancer compared with conventional chemotherapy using cisplatin and 5-fluorouracil: a retrospective study. *Dis Esophagus* 2008; 21: 496-501.
- [30] Jin J, Xu X, Wang F, Yan G, Liu J, Lu W, Li X, Tucker SJ, Zhong B, Cao Z and Wang D. Second-line combination chemotherapy with docetaxel and nedaplatin for cisplatin-pre-treated refractory metastatic/recurrent esophageal squamous cell carcinoma. *J Thorac Oncol* 2009; 4: 1017-1021.
- [31] Kanai M, Matsumoto S, Nishimura T, Shimada Y, Watanabe G, Kitano T, Misawa A, Ishiguro H, Yoshikawa K, Yanagihara K, Teramukai S, Mitsumori M, Chiba T, Sakai Y and Fukushima M. Retrospective analysis of 27 consecutive patients treated with docetaxel/nedaplatin combination therapy as a second-line regimen for advanced esophageal cancer. *Int J Clin Oncol* 2007; 12: 224-227.
- [32] Osaka Y, Takagi Y, Hoshino S, Tachibana S, Tsuchida A and Aoki T. Combination chemotherapy with docetaxel and nedaplatin for recurrent esophageal cancer in an outpatient setting. *Dis Esophagus* 2006; 19: 473-476.
- [33] Shukuya T, Yamanaka T, Seto T, Daga H, Goto K, Saka H, Sugawara S, Takahashi T, Yokota S, Kaneda H, Kawaguchi T, Nagase S, Oguri T, Iwamoto Y, Nishimura T, Hattori Y, Nakagawa K, Nakanishi Y, Yamamoto N; West Japan Oncology Group. Nedaplatin plus docetaxel versus cisplatin plus docetaxel for advanced or relapsed squamous cell carcinoma of the lung (WJOG5208L): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2015; 16: 1630-1638.
- [34] Zhang F, Wang Y, Wang ZQ, Sun P, Wang DS, Jiang YX, Zhang DS, Wang FH, Xu RH and Li YH. Efficacy and safety of cisplatin-based versus nedaplatin-based regimens for the treatment of metastatic/recurrent and advanced esophageal squamous cell carcinoma: a systematic review and meta-analysis. *Dis Esophagus* 2017; 30: 1-8.
- [35] Kuwahara A, Yamamori M, Nishiguchi K, Okuno T, Chayahara N, Miki k, Tamura T, Inokuma T, Takemoto Y, Nakamura T, Kataoka K and Sakaeda T. Replacement of cisplatin with nedaplatin in a definitive 5-fluorouracil/cisplatin-based chemoradiotherapy in Japanese patients with esophageal squamous cell carcinoma. *Int J Med Sci* 2009; 6: 305-311.
- [36] Yamashita H, Nakagawa K, Tago M, Igaki H, Nakamura N, Shiraishi K, Sasano N and Ohtomo K. Radiation therapy combined with cisplatin-glycolatoplatinum (nedaplatin) and 5-fluorouracil for Japanese stage II-IV esophageal cancer compared with cisplatin plus 5-fluorouracil regimen: a retrospective study. *Dis Esophagus* 2006; 19: 15-19.
- [37] Rodriguez N, Algara M, Foro P, Lacruz M, Reig A, Membrive I, Lozano J, Lopez JL, Quera J, Fernandez-Velilla E and Sanz X. Predictors of acute esophagitis in lung cancer patients treated with concurrent three-dimensional conformal radiotherapy and chemotherapy. *Int J Radiat Oncol Biol Phys* 2009; 73: 810-817.
- [38] Wei X, Liu HH, Tucker SL, Liao Z, Hu C, Mohan R, Cox JD and Komaki R. Risk factors for acute esophagitis in non-small-cell lung cancer patients treated with concurrent chemotherapy and three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2006; 66: 100-107.
- [39] Gandara DR, Chansky K, Albain KS, Leigh BR, Gaspar LE, Lara PN Jr, Burris H, Gumerlock P, Kuebler JP, Bearden JD 3rd, Crowley J, Livingston R; Southwest Oncology Group. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003; 21: 2004-2010.
- [40] Komaki R, Seiferheld W, Ettinger D, Lee JS, Movsas B and Sause W. Randomized phase II chemotherapy and radiotherapy trial for patients with locally advanced inoperable non-small cell lung cancer: long-term follow-up of RTOG 92-04. *Int J Radiation Oncology Biol Phys* 2002; 53: 548-557.
- [41] Wang B, Zhao B, Pang LP, Zhao YD, Guo Q, Wang JW, Zheng YC, Zhang XH, Liu Y, Liu GY, Guo WG, Wang C, Li ZH, Mao XJ, Yu B, Ma LY and Liu HM. LPE-1, an orally active pyrimidine

- derivative, inhibits growth and mobility of human esophageal cancers by targeting LSD1. *Pharmacol Res* 2017; 122: 66-77.
- [42] Dutton SJ, Ferry DR, Blazeby JM, Abbas H, Dahle-Smith A, Mansoor W, Thompson J, Harrison M, Chatterjee A, Falk S, Garcia-Alonso A, Fyfe DW, Hubner RA, Gamble T, Peachey L, Davoudianfar M, Pearson SR, Julier P, Jankowski J, Kerr R and Petty RD. Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *Lancet Oncol* 2014; 15: 894-904.
- [43] De Silva N, Schulz L, Paterson A, Qain W, Secrier M, Godfrey E, Cheow H, O'Donovan M, Lao-Sirieix P, Jobanputra M, Hochhauser D, Fitzgerald R and Ford H. Molecular effects of Lapatinib in the treatment of HER2 overexpressing oesophago-gastric adenocarcinoma. *Br J Cancer* 2015; 113: 1305-1312.
- [44] Hecht JR, Bang YJ, Qin SK, Chung HC, Xu JM, Park JO, Jeziorski K, Shparyk Y, Hoff PM, Sobrero A, Salman P, Li J, Protsenko SA, Wainberg ZA, Buyse M, Afenjar K, Houe V, Garcia A, Kaneko T, Huang Y, Khan-Wasti S, Santillana S, Press MF and Slamon D. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC—a randomized phase III trial. *J Clin Oncol* 2016; 34: 443-451.