Cancer Chemother Pharmacol (2008) 61:33–38
DOI 10.1007/s00280-007-0441-8

ORIGINAL ARTICLE

Phase II clinical study of gemcitabine in the treatment of patients with advanced nasopharyngeal carcinoma after the failure of platinum-based chemotherapy

Li Zhang · Yang Zhang · Pei-Yu Huang · Fei Xu · Pei-Jian Peng · Zhong-Zhen Guan

Received: 17 October 2006 / Accepted: 14 February 2007 / Published online: 20 March 2007

Abstract
Purpose This study was designed to evaluate the anti-tumor activity and toxicity profile of gemcitabine in the treatment of patients with advanced nasopharyngeal carcinoma (NPC) who had been pretreated with platinum-based chemotherapy.
Method This is an open label, single arm phase II trial. All patients were treated with single agent of gemcitabine. Gemcitabine was given in the dosage of 1.0 g/m^2 on days 1, 8, 15, each cycle repeated every 4 weeks. Gemcitabine was added to 100 ml normal saline infused over 30 min.
Result About 32 patients were enrolled in this trial. Thirty patients were assessable for response to treatment. Fourteen patients had a partial response (PR), giving an overall response rate of 43.8% (14/32); 9 patients had stable disease (28.1%) and 7 progressed disease (21.9%). The median time to progression was 5.1 months and median survival time was 16 months, 1 year survival rate was 67%, 2 year overall survival rate was 12%. A total of 11 patients (34.4%) experienced grade 3 and 4 toxicity and the main toxicity was myelosuppression. the non-hematology toxicity was minimal.
Conclusion The effectiveness of gemcitabine was higher and side effects were minimal in advanced NPC patients after platinum-based chemotherapy failed.

This paper was presented in part at the 40th Annual Meeting of the American Society of Clinical Oncology, 2004.

L. Zhang (✉) · Y. Zhang · P.-Y. Huang · F. Xu · P.-J. Peng · Z.-Z. Guan
Department of Medical Oncology,
Cancer Center of Sun Yat-Sen University,
651# Dongfeng Road East,
Guangzhou, 510060, People's Republic of China
e-mail: zhangli6@mail.sysu.edu.cn

Keywords Gemcitabine · Nasopharyngeal carcinoma

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors of head and neck in the South-east Asia. About 90% of them are undifferentiated or poorly differentiated squamous cell carcinoma, which are highly malignant, fast growing and with high occurrence of lymph node and distant metastasis. Seventy-five percent of new diagnostic cases are III or IV stage. Radiotherapy is one of the most common used treatment methods for NPC. The curative rate is around 50%. The failure in the treatment is mainly due to distant metastasis and reoccurrence [1].

In the recent years, chemotherapy in NPC has made a very big progress, it plays vital role both in combined modality of chemo-radiotherapy for locally advanced disease as well as in treatment of metastatic disease. Platinum-based combination regime (typically cisplatin +5-fluorouracil) is the most commonly used chemotherapy regime [2]. There is no consensus on secondline chemotherapy treatment for patients who are already treated with platinum-based regime. For that reason, there is an urgent need to find new effective drug.

Gemcitabine (Gemzar; Eli-lilly Pharmaceuticals, Inc, USA) is a pyrimidine analog, a ribonucleotide reductase inhibitor that competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA. Gemcitabine had been proven its efficiency in many types of tumors like NSCLC, pancreatic and breast cancer [3]. But there is few report on treatment of NPC using gemcitabine. The goal of this study is to evaluate the efficacy and safety profile of gemcitabine in advanced NPC patients who failed or progressed after treatment with platinum-based chemotherapy. The preliminary

result of this study had partially presented at the 40th Annual Meeting of the American Society of Clinical Oncology [4].

Patients and materials

Patients

Eligibility criteria consisted of (1) pathologically confirmed advanced (stage IV) or metastatic NPC; (2) previously treated with platinum-based chemotherapy; (3) performance status 0–2; (4) life expectancy of more than 12 weeks; (5) adequate bone marrow (WBC $> 4.0 \times 10^9\,l^{-1}$, Pt $> 100 \times 10^9\,l^{-1}$), renal, and hepatic function. (6) More than 3 weeks must have elapsed since previous radiotherapy or chemotherapy. (7) Bidimensional measurable disease outside a previous radiation port was required. (8) Patients who agreed to receive gemcitabine treatment and sign informed consent.

Patients with CNS metastasis, uncontrolled infection or life threatening medical condition, pregnant and lactating women, PS > 2 were excluded from the study. Patients who did not agree to receive gemcitabine treatment were also excluded from this study. The study protocol was approved by the Research Ethics Committee of the Cancer Center of Sun Yat-Sen University.

Treatment plan

Gemcitabine 1.0 g/m^2 was added to 100 ml normal saline and infused over 30 min given on 1, 8, 15 days following 2 weeks rest. Treatment was repeated every 4 weeks. Antiemetic medication consisted of 5-HT3 receptor antagonists administered before chemotherapeutic treatment. Treatment will be continued until patient presence of disease progression.

In case of neutrophils $<1.5 \times 10^9\,l^{-1}$ or platelets $<100 \times 10^9\,l^{-1}$ in day 8 or day 15, the chemotherapy was withheld until normal values were re-established. If the blood count did not recover after 7 days, the patient would skip the dose. The dose of gemcitabine would be reduced by 20% for patients whom experienced CTC Grade 3 or 4 hematological toxicity in the prior cycle. In this research, preventive G-CSF or GM-CSF was not used.

Clinical assessment

All patients underwent baseline chest radiograph or computed tomography (CT) of thorax, CT scan of nasopharynx and upper abdomen within 4 weeks prior to day 1 of the first cycle of chemotherapy. Bone scan was performed for patients with symptoms suggestive metastatic disease involving bone. Laboratory investigation including complete blood count, renal function tests, liver function tests, serum calcium, prothrombin time and blood glucose were performed within the week preceding treatment initiation. Completed blood count and renal/liver function tests were repeated weekly and monthly during chemotherapy, respectively.

Tumor size was assessed via computed tomography, magnetic resonance imaging, or chest X-ray every two cycles. Standard WHO response criteria were used to determine tumor response and disease progression [5]. Objective tumour response was evaluated every two cycles of chemotherapy or when clinical progression was suspected by repeating baseline staging procedures as needed. Confirmatory imaging must be performed at least 4 weeks after the first documented response. Toxicity was graded according to the National Cancer Institute common toxicity criteria (NCI-CTC 2.0 version).

All enrolled patients were followed every 2 month until to death. Time to disease progression was defined as the time from randomization to the date of documentation of disease progression. Overall survival was measured from the date of randomization to the date of death.

Statistics

The hoped-for response rate was assumed to about 20%. Half of the confidential interval was15% and the result were considered unacceptable if response rate was less than 5%. To distinguish from an unacceptable outcome with 80% power and less than 5% type I error, 27 patients would be necessary. Objective responses were calculated as relative rates with their 95% confidence limits (95% CL), and reported according to an intent to treat analysis (ITT). Therefore, non-evaluable patients were considered as treatment failures. Percentages were approximated to the nearest unit. TTP, Time to disease progression and OS were assessed according to the product-limit method described by Kaplan–Meier. One and 2 year survival rate were assessed according to the Life-Table.

Result

About 32 patients were included in this study. In 32 patients, 28 were male and 4 were female; Median age was 43 years (range 26–65); 31 of them have had distant metastasis; 3 patients were WHO Type 1 keratinizing squamous cell carcinoma (SCC), 29 patients were WHO Type 2 non-keratinizing squamous cell carcinoma and all were type 2B (undifferentiated non-keratinizing carcinoma). Twenty-seven patients were previously treated with radiotherapy. Median previously received chemotherapy cycles were four

cycles (range 2–11). Adjuvant or concurrent platinum chemotherapy 8 patients, previously received 1 regime chemotherapy 15 patients, 2 regimen 7 patients, >2 regimens 2 patients. Previously chemotherapy regimes include cisplatin + 5-fluorouracil, and cisplatin + capecitabine, paclitaxel + carboplatin. The interval between starting this trial and the last prior chemotherapy ≤3 months was in 21 (65.6%) patients and >3 months in 11 (34.4%) patients, with a median of 2 months (range 1–14). Patient Characteristics are shown in Table 1.

Response and survival

About 105 cycles of chemotherapy were given to 32 patients (1–8 cycles), average 3.5 cycles (median 4 cycles). Two patients just received one cycle of chemotherapy and loss follow up so were not evaluated for the effect. Gemcitabine does were reduced, omited or delayed in 12 patients (8 patients because of neutropenia and 4 patients because of increase in aminotransferase). The dose intensity of gemcitabine was 670 mg/m^2·week. Among 32 cases, no complete remission (CR), partial remission (PR) occurred in 14 cases (43.8, 95% CL 26.6–61.0%), stable disease (SD) in 9 cases (28.1%), progressive disease (PD) in 7 cases (21.9%), not evaluable in 2 cases (6.3%). Among the 8 patients previously received adjuvant or concurrent platinum chemotherapy, gemcitabine was given as first-line chemotherapy, there were 50% (4/8) PR, 12.5% (1/8) SD, 37.5% (3/8) PD; the previously received 1 regimen chemotherapy patients which gemcitabine was used as second-line therapy, there were 46.7% (7/15) PR, 33.3% (5/15) SD, 6.7% (1/15) PD; in patients ≥2 regimens chemotherapy, there were 33.3% (3/9) PR, 33.3% (3/9) SD, 33.3% (3/9) PD. In our study, of the 3 Type 1 keratinizing SCC patients, 2 attained PR, 1 SD; in the 29 WHO Type 2 nonkeratinizing squamous cell carcinoma patients, the response rate was 41.4% (12/29) (Table 2; Fig. 1).

Table 1 Patient characteristics

Total patient enrolled	32
Evaluated patients	30
Male/female	28/4
Age (median)	26–65 (43)
Histology (WHO 1992)	
Type 1 keratinizing SCC	3
Type 2 nonkeratinizing SCC	29
2A	0
2B	29
Presence of distant metastasis	
Yes	31
No	1
Distant disease site	
Lung	21
Liver	12
Bone	4
Other sites	5
Previously treatment	
Radiotherapy (RT)	27
Chemotherapy (CT)	32
Adjuvant or concurrent	8
1	15
2	7
>3	2
Previously CT cycles (median)	2–11 (4)

With a median follow-up time of 24 months, median time to progression was 5.1 months (range 0.5–11.2); median survival time was 16.0 months (range 0.5–31.5). Kaplan–Meier curves of time to disease progression and overall survival are shown in Figs. 2 and 3. One year survival rate was 67%; 2 year overall survival rate was 12%.

Figure 1 shows computed tomography scans of a PR. These scans are of a 38-year-old Chinese male diagnosed with stage IIIB NPC (nonkeratinizing squamous cell carcinoma) in January 2002. Patient was treated with radiotherapy following diagnosis. The patient developed liver metastasis at October 2002. After four cycles of cisplatin plus 5-fluoruracial, the response evaluation showed progression disease. The first image is at baseline, and the second image was taken after four cycles of therapy (Gemcitabine 1,600 mg IV drip D1, D8, D15). He remains on study after 8 cycles of therapy with a PR.

Toxicity

About 32 patients were assessable for toxicity. Grade 3 and 4 toxicity occurred in 34.4% (11/32) patients, mainly were hematological toxicity, leucopoenia and neutropenia, and non-hematological toxicities were minimal. Adverse reaction is shown in Table 3.

During the treatment, leucopenia and neutropenia occurred in 71.9% (23/32) and 65.6% (21/32) patients, respectively, but were not serious. Both Grade 3/4 leucopenia and neutropenia occurred only in 18.8% (6/32) patients, but no neutropenic fever and all patients' CBC recovery to normal within 2 weeks; only in two patients G-CSF was used. Anemia and thrombocytopenia occurred in 25.0% (8/32) patients, respectively. No blood transfusion needed in any patient. Increase in aminotransferase and nausea and vomiting was the mostly occurred non-hematological toxicity and occurred in 28.1% (9/32) and 34.4% (11/32) patients, respectively. Grade 3 and 4 increase in aminotransferase occurred in 6.3% (2/32) and 3.1% (1/32) patients, respectively. Nausea and vomiting were mild (Grade 1 and 2). About 62.5% (20/32) were treated with

Table 2 Effects of gemcitabine according patient characteristics

	PR (%)	SD (%)	PD (%)	NA (%)	All
Total	14 (43.8)	9 (28.1)	7 (21.9)	2 (6.3)	32
Previously chemotherapy					
Adjuvant or concurrent	4 (50.0)	1 (12.5)	3 (37.5)	0 (0.0)	8
1 regiment	7 (46.7)	5 (33.3)	1 (6.7)	2 (13.3)	15
≥2 regiment	3 (33.3)	3 (33.3)	3 (33.3)	0 (0.0)	9
Histology (WHO 1992)					
Type 1 keratinizing SCC	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	3
Type 2 nonkeratinizing SCC	12 (41.4)	8 (27.6)	7 (24.1)	2 (6.9)	29
Distant disease site					
Lung	9 (42.9)	5 (23.8)	6 (28.6)	1 (4.8)	21
Liver	6 (50.0)	1 (8.3)	5 (41.7)	0 (0.0)	12

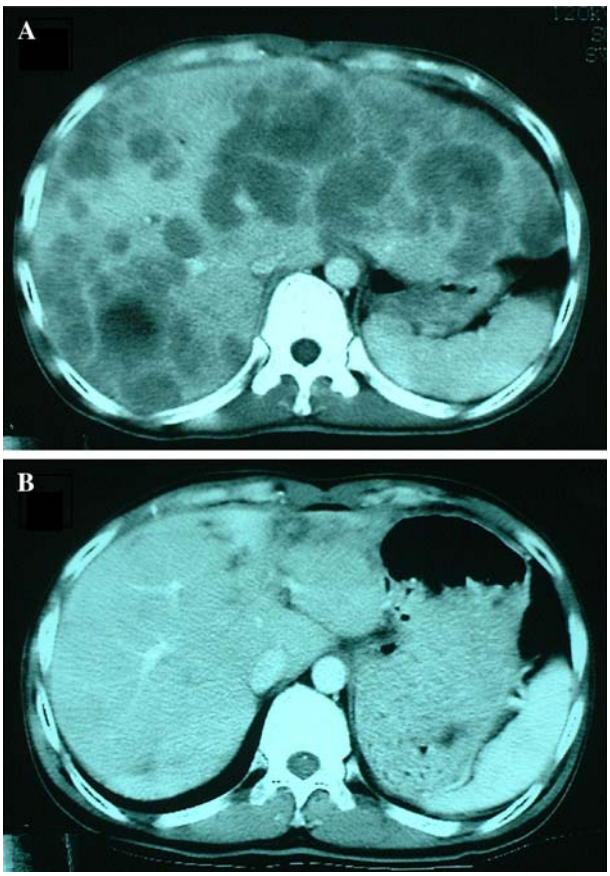

Fig. 1 Example of response to treatment with gemcitabine. **a** Pretreatment with gemcitabine (13 January 2003). **b** Post-treatment with gemcitabine (08 May 2003). Computed tomography scans of a 38-year-old Chinese male with NPC liver metastasis. Image **a** was taken at baseline, and image **b** was taken after four cycles of Gemcitabine (1,600 mg IV drip, D1, D8, and D15)

ondencentron, 31.3% (10/32) with metoclopramide. Rashes occurred in 15.6% (5/32) patients. Non-infective drug related fever was in 18.8% (6/32) patients. Alopecia was 6.3% (2/32) and all were Grade 1 and 2.

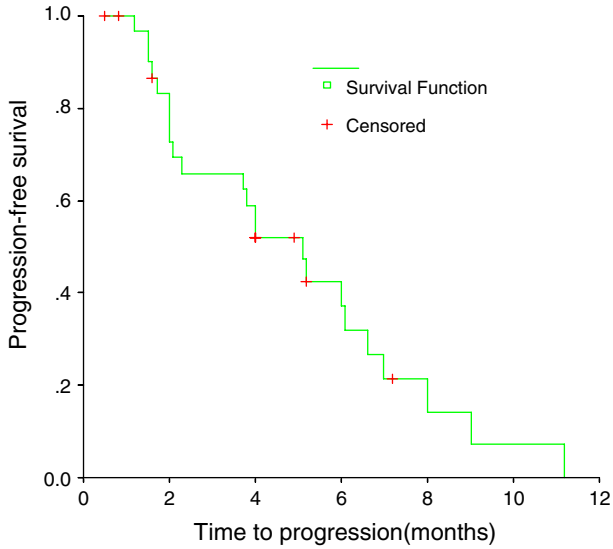

Fig. 2 Kaplan–Meier, curve of time to disease progression

Discussion

NPC is a chemotherapy sensitive cancer. Cisplatin, carboplatin, 5-fluorouracil, methotrexate, cyclophosphamide, bleomycin, adriamycin are commonly used single agent drugs. Response rate is around 30%; median response duration is 3–6 months [2]. A lot of clinical researches revealed combined chemotherapy has a better result than single agent. Cisplatin containing chemotherapy regime shows better response and became the most commonly used regime. Patients who failed platinum regime chemotherapy, there is no standard regimen till now. Some report has showed that taxens, Vinorelbine, irinotecan were effective drugs [6–9].

Gemcitabine is a pyrimidine analog, a ribonucleotide reductase inhibitor that competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA. It is clinically proven that it is effective against many type of tumor like non-small cell lung cancer, breast cancer and pancre-

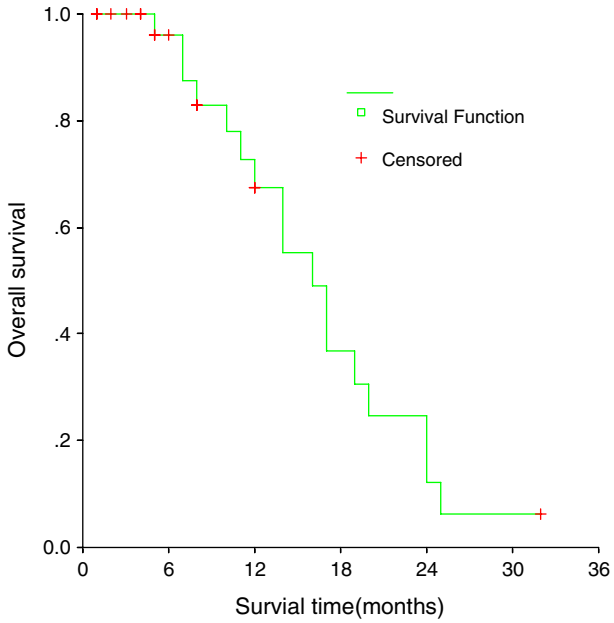

Fig. 3 Kaplan–Meier, curve of and overall survival

atic cancer. Gemcitabine also has high single agent activity in NPC. Foo [10] reported one research where metastatic NPC patient were treated with gemcitabine alone, gemcitabine 1,250 mg/m^2 was given on days 1 and 8 of a 21 day cycle. Twenty-five chemo naive and 27 previously treated patients were enrolled. The overall response rate was 28% for the chemo naive and 48% for previously treated patients. For the chemo naive patients the median time to progression and median overall survival time were 3.6 and 7.2 months, respectively, and for the previously treated patients the median time to progression and median overall survival time were 5.1 and 10.5 months, respectively. Ma [11] also reported the experience in Princess Margaret hospital, 32 patients with NPC were treated with gemcitabine or combined with cisplatin (GC). In the single agent group, the overall response rate was 34%; in the combined group, the response rate was 64%. The median duration of response for the gemcitabine and GC patients was 17 and 24 weeks and the 1 year survival rate was 48 and 69%, respectively. Hematologic toxicity was dose limiting but uncomplicated. Although direct comparison of the results between our study and other trials is difficult because the patient characteristics and dosage of gemcitabine are different, the response rate (43.8%) in our study was comparable with the response rate (48%) for previously treated patients in Foo et al. [10] study. It appears to be relative non-cross-resistant with other active agents. The response observed in 5 of 14 patients who had progressed within 3 months of receiving platinum-based regimen. In current study, all patients were diagnoses in endemic area and relatively young. It still remains unclear whether the results obtained from this study can be extrapolated to non-endemic areas which older cohorts patients are more common.

Gemcitabine is well tolerated. The main toxicity of gemcitabine is neutropenia. In Foo's research, the toxicities greater than or equal to grade 3 occurred in 15 (60%) chemo naive and 13 (48%) previously treated patients. Neutropenia was uncommon in chemo naive patients, but occurred in 37% of previously treated patients. In our research it was not severe, Grade 3/4 leucopenia and neutropenia occurred only in 34.4% patients, but no neutropenic fever, only in two patients G-CSF was used, reflects the given dose is suitable to patients.

Combining gemcitabine with other agents would be the next logical step in enhancing its chemotherapeutic effectiveness against NPC. Ngan et al. [12] reported a phase II result of clinical trial in which gemcitabine with cisplatin (Gemcitabine 1,000 mg/m^2 d1, d8, d15; cisplatin 50 mg/m^2 d1, d8 q28 days) were used in the treatment of metastatic or recurrent NPC patients. Among 44 cases, the overall response rate was 73%, CR 15%. On the basis of these results, we will try to design a study to investigate the combination of gemcitabine with cisplatin used as first line regimen in the treatment of metastatic NPC patients.

Table 3 Adverse reactions

Adverse reaction	WHO grade				
	0(%)	I (%)	II (%)	III (%)	IV (%)
Nausea and vomiting	21 (65.6)	9 (28.1)	2 (6.3)	0 (0.0)	0 (0.0)
Allergy	25 (78.1)	5 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)
Leucopenia	7 (21.9)	10 (31.2)	7 (21.9)	5 (15.6)	1 (3.1)
Neutropenia	9 (28.1)	5 (15.6)	10 (31.2)	5 (15.6)	1 (3.1)
Anemia	22 (68.8)	6 (18.8)	1 (3.1)	1 (3.1)	0 (0.0)
Thrombocytopenia	22 (68.8)	5 (15.6)	2 (6.3)	1 (3.1)	0 (0.0)
Fever without infection	24 (75.0)	3 (9.4)	3 (9.4)	0 (0.0)	0 (0.0)
Alopecia	28 (88.0)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Increase aminotransferase	22 (68.8)	3 (9.4)	1 (3.1)	2 (6.3)	1 (3.1)

Conclusion

The effectiveness of gemcitabine was higher and side effects were minimal in advanced NPC patients after platinum-based chemotherapy failed. Still further research should be done to comparing gemcitabine + cisplatin and cisplatin + 5-fluorouracil as a first line chemotherapy regime in the advanced NPC.

Acknowledgments We thank Eli Lilly Corporation for providing free samples of gemcitabine for our study. We also thank all patients and their families for their willingness to take part in this study.

References

1. Tang C-Y (1993) Modern oncology. Shanghai University of medical science, Shanghai, pp 586–610
2. Zhou JC (1998) Practical medical oncology. People's Health Publisher, Beijing, pp 508–513
3. Barton-Burke M (1999) Gemcitabine: a pharmacologic and clinical overview (review). Cancer Nurs 22:176–183
4. Zhang L, Zhang Y, Guan ZZ (2004) Phase II clinical study of gemcitabine single agent for patients with advanced nasopharyngeal carcinoma (NPC) who failed to first line platinum-based chemotherapy. Proc Am Soc Clin Oncol 23:5612a
5. Green S, Weiss G (1992) Southwest oncology group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs 10:239–253
6. Chan AT, Teo PM, Leuang TW et al (1998) The role of chemotherapy in the management of nasopharyngeal carcinoma. Cancer 82(6):1003–1012
7. Zhang L, Jiang WQ, Xu RH et al (2000) Clinical study of paclitaxel in the treatment of nasopharyngeal carcinoma. Chin J Cancer 19(8):811–813
8. Chang JT, Ko JY, Hong RL (2004) Recent advances in the treatment of nasopharyngeal carcinoma. J Formos Med Assoc 103(7):496–510
9. Poon D, Chowbay B, Leong SS et al (2004) Singapore phase II study of irinotecan (CPT-11) as salvage therapy for advanced nasopharyngeal carcinoma (NPC). ASCO Ab5576
10. Foo KF, Tan EH, Leong SS et al (2002) Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. Ann Oncol 13:150–156
11. Ma BB, Tannock IF, Pond GR et al (2002) Chemotherapy with gemcitabine-containing regimens for locally recurrent or metastatic nasopharyngeal carcinoma. Cancer 95:2516–2523
12. Ngan RKC, Yiu HHY, Lau WH, Yau S et al (2002) Combination gemcitabine and cisplatin chemotherapy for metastatic or recurrent nasopharyngeal carcinoma. Ann Oncol 13:1252–1258