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SALVAGE REGIMENS FOR PEDIATRIC PATIENTS WITH RELAPSED NASOPHARYNGEAL CARCINOMA

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Abstract

There is no established salvage regimen for pediatric patients with relapsed nasopharyngeal carcinoma (NPC) and outcomes are dismal. We performed a multicenter retrospective review to determine outcomes after first salvage therapy for pediatric patients with relapsed NPC. Fourteen patients were treated with varied regimens. Two of the 14 patients received oxaliplatin-containing regimens and achieved a long-term complete response. Although definitive recommendations cannot be made based on outcomes for 14 patients who received varied regimens, we discuss justification for an oxaliplatin-containing regimen in combination with gemcitabine as a reasonable choice for first line salvage therapy for pediatric patients with relapsed NPC.

Keywords

Pediatric; NPC; nasopharyngeal carcinoma; relapse; chemotherapy

INTRODUCTION

Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy has resulted in event free survival (EFS) rates of approximately 70–80% for pediatric patients with nasopharyngeal carcinoma (NPC).^{1–7} However, outcomes for children with relapsed NPC remain poor.^{2,3} The majority of patients with relapsed NPC present with distant metastatic disease.² Radiation therapy (XRT) alone is often inadequate to treat relapsed NPC because most relapses occur at distant sites. Furthermore, XRT doses needed to treat distant metastatic NPC could result in severe organ toxicity. Thus, chemotherapy is required to treat the majority of pediatric patients with relapsed NPC. Despite the need for salvage chemotherapy to treat pediatric patients with relapsed NPC, no standard regimen exists for this patient population. The objective of this study was to evaluate salvage chemotherapy

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CONFLICT OF INTEREST STATEMENT

SG has patent applications in the field of cell and gene therapy for cancer, and receives research support from TESSA Therapeutics.

regimens used to treat children with relapsed NPC across 3 institutions and identify agents with the highest activity in this setting.

METHODS

Data were obtained by retrospective review of medical records from pediatric patients with relapsed or progressive NPC at Texas Children's Cancer Center, St. Jude Children's Research Hospital, and Children's Healthcare of Atlanta, and one patient identified by literature review.^{8,9} Institutional review boards at these institutions approved conduct of the study. Patients < 21 years of age at first relapse or progression, diagnosed between January 1990 and December 2015 were included. A standard data collection form was used to obtain clinical information including age at first relapse or progression, site(s) of first relapse or progression, chemotherapy for first relapse or progression, XRT for first relapse or progression, vital status at last follow up, as well as EFS and overall survival (OS) after chemotherapy for first relapse or progression. EFS and OS outcomes were analyzed using the Kaplan-Meier method.

RESULTS

Fourteen pediatric patients were diagnosed with relapsed or progressive NPC at a median age of 16 years (range 11–18 years). Eleven patients were male and three female. Six patients identified as Black, 6 White, 1 Hispanic, and 1 mixed race. All patients had stage III or IV disease at initial diagnosis and were treated with upfront cisplatin-based chemotherapy in combination with XRT. The median time to first relapse or progression was 9.5 months (range 6 – 27 months) (Supplementary Table S1). Sites of initial relapse included bone (n=8), lung (n=5), lymph node (n=3), soft tissue (n=2), and 1 each in liver, nasopharynx and eyes. Treatment and outcomes for the 14 patients are summarized in Table 1.

At first relapse or progression, 2 patients were treated with oxaliplatin in combination with gemcitabine or doxorubicin. Both patients treated with oxaliplatin-containing regimens achieved complete remission and were alive without disease at last follow-up.

Seven patients were treated with carboplatin plus a taxane (paclitaxel or docetaxel). Six of these 7 patients had disease progression after first salvage therapy. The seventh patient received XRT and Epstein-Barr virus-specific T lymphocytes (EBVSTs) as part of first relapse treatment and achieved long-term remission. Two of these 7 patients achieved a remission after subsequent salvage therapy that included EBVSTs.

One patient with isolated occipital bone relapse was alive without disease after surgical resection followed by vincristine, doxorubicin, cyclophosphamide, irinotecan and EBVSTs. Five patients received XRT as part of first salvage therapy and 1 remained alive without disease after multi-modality treatment. One patient achieved complete remission and remains alive without disease after nivolumab monotherapy. Three patients received other regimens and died after disease progression. Overall, seven patients were alive after a median follow-up of 21.5 months. Three-year EFS and OS were 34% and 44% respectively (Fig. 1).

DISCUSSION

These data demonstrate that disease remission and long-term survival are possible for some pediatric patients with relapsed NPC. Although definitive recommendations cannot be made based on outcomes for 14 patients who received varied regimens, an oxaliplatin-containing regimen in combination with gemcitabine would be a reasonable choice for first line salvage therapy for pediatric patients with relapsed NPC.

Cisplatin and gemcitabine is considered by many as the standard first line treatment for adults with relapsed or metastatic NPC.¹⁰ This choice is based on data from a large, multi-center, phase III, randomized clinical trial, which demonstrated superiority of cisplatin plus gemcitabine over cisplatin plus 5-fluorouracil for first treatment of adults with relapsed or metastatic NPC.¹¹ Patients treated with cisplatin and gemcitabine had an objective response rate (ORR) of 64% (15 complete response (CR), 101 partial response (PR)), disease control rate (DCR) of 90%, and median PFS of 7.0 months. Patients treated with cisplatin and 5-fluorouracil had an ORR of 42% (5CR, 71PR), DCR of 86%, and median PFS of 5.6 months. Notably, nearly half the patients received no chemotherapy prior to enrollment on this trial. Given that almost all pediatric patients with NPC are treated with up front cisplatin-containing regimens, an alternative to cisplatin would be ideal to treat pediatric patients with relapsed disease.

Oxaliplatin is a third-generation platinum that lacks cross resistance to cisplatin *in vitro*.¹² Compared to cisplatin, oxaliplatin lacks ototoxic and nephrotoxic side effects. Myelosuppression due to oxaliplatin is less when compared to carboplatin. Efficacy of oxaliplatin plus gemcitabine (gem/ox) is supported by adult patient data. In a multi-center phase II study, gem/ox was evaluated as first salvage therapy for 42 patients with relapsed or metastatic NPC.¹³ Patients received a mean 10 cycles of gem/ox resulting in an ORR of 56% (1CR, 22PR) and DCR of 88%. After median follow up of 14.8 months, patients had a median time to progression of 8.9 months. Combining our experience with adult trials, gem/ox should be considered for pediatric patients with relapsed NPC.

Consolidation with autologous EBVSTs should also be considered for pediatric patients with relapsed EBV-positive NPC, although availability of this treatment is currently limited. EBVST activity against relapsed, progressive and metastatic NPC has been shown in multiple trials. In a phase II trial, 35 patients with EBV-positive relapsed or metastatic NPC were treated with gemcitabine plus carboplatin followed by up to 6 doses of EBVSTs.¹⁴ Efficacy of EBVSTs was based on pre-EBVST and post-EBVST imaging and demonstrated an ORR of 43% (2 continued CR, 13PR), and DCR of 63%. In a separate phase I/II trial for patients with advanced stage, or relapsed/refractory EBV-positive NPC, 23 patients (8 in remission and 15 with active disease) were treated with EBVSTs.¹⁵ Of the 8 patients in remission, 5 had continued CR. For patients with active disease the ORR was 47% (5CR, 2PR) and DCR 67%, with PFS at 1 and 2 years of 65% and 52% respectively.

One pediatric patient from our study was treated with nivolumab monotherapy and achieved complete remission. Evidence for benefit of targeting the PD-1 pathway for patients with NPC has been demonstrated previously.^{16,17} In the KEYNOTE-028 trial, twenty-seven

patients with locally advanced, relapsed or metastatic, PD-L1 positive NPC were treated with pembrolizumab, and had an ORR of 26% (0CR, 7PR), DCR of 78%, and median PFS of 6.5 months.¹⁶

In conclusion, long-term remission can be achieved in some children with relapsed NPC using conventional agents. Combining our experience with adult trials, gem/ox should be considered for pediatric patients with relapsed NPC. XRT should be considered in consultation with a radiation oncologist specializing in treatment of children. EBVST should also be considered in this setting, and the role of immune checkpoint inhibitors investigated in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation Table

NPC	Nasopharyngeal carcinoma
EFS	Event free survival
XRT	Radiation therapy
OS	Overall survival
EBVST(s)	Epstein-Barr Virus-specific T lymphocyte(s)
ORR	Objective response rate
CR	Complete response
PR	Partial response
DCR	Disease control rate
Gem/ox	Oxaliplatin plus gemcitabine

References

1. Ozyar E, Selek U, Laskar S, et al. Treatment results of 165 pediatric patients with non-metastatic nasopharyngeal carcinoma: a Rare Cancer Network study. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2006;81(1):39–46. [PubMed: 16965827]
2. Cheuk DK, Billups CA, Martin MG, et al. Prognostic factors and long-term outcomes of childhood nasopharyngeal carcinoma. *Cancer*. 2011;117(1):197–206. [PubMed: 20737561]
3. Casanova M, Bisogno G, Gandola L, et al. A prospective protocol for nasopharyngeal carcinoma in children and adolescents: the Italian Rare Tumors in Pediatric Age (TREP) project. *Cancer*. 2012;118(10):2718–2725. [PubMed: 21918965]

4. Casanova M, Ozyar E, Patte C, et al. International randomized phase 2 study on the addition of docetaxel to the combination of cisplatin and 5-fluorouracil in the induction treatment for nasopharyngeal carcinoma in children and adolescents. *Cancer chemotherapy and pharmacology*. 2016;77(2):289–298. [PubMed: 26666649]
5. Rodriguez-Galindo C, Wofford M, Castleberry RP, et al. Preradiation chemotherapy with methotrexate, cisplatin, 5-fluorouracil, and leucovorin for pediatric nasopharyngeal carcinoma. *Cancer*. 2005;103(4):850–857. [PubMed: 15641027]
6. Buehrlen M, Zwaan CM, Granzen B, et al. Multimodal treatment, including interferon beta, of nasopharyngeal carcinoma in children and young adults: preliminary results from the prospective, multicenter study NPC-2003-GPOH/DCOG. *Cancer*. 2012;118(19):4892–4900. [PubMed: 22359313]
7. Orbach D, Brisse H, Helfre S, et al. Radiation and chemotherapy combination for nasopharyngeal carcinoma in children: Radiotherapy dose adaptation after chemotherapy response to minimize late effects. *Pediatric blood & cancer*. 2008;50(4):849–853. [PubMed: 17973328]
8. Venkatramani R, Mascarenhas L. Successful treatment of recurrent metastatic nasopharyngeal carcinoma with oxaliplatin and doxorubicin. *Journal of pediatric hematology/oncology*. 2014;36(5):e307–309. [PubMed: 24276035]
9. Mascarenhas L, Malogolowkin M, Armenian SH, Sposto R, Venkatramani R. A phase I study of oxaliplatin and doxorubicin in pediatric patients with relapsed or refractory extracranial non-hematopoietic solid tumors. *Pediatric blood & cancer*. 2013;60(7):1103–1107. [PubMed: 23335436]
10. Lee V, Kwong D, Leung TW, Lam KO, Tong CC, Lee A. Palliative systemic therapy for recurrent or metastatic nasopharyngeal carcinoma - How far have we achieved? Critical reviews in oncology/hematology. 2017;114:13–23. [PubMed: 28477740]
11. Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet (London, England)*. 2016;388(10054):1883–1892.
12. Rixe O, Ortuzar W, Alvarez M, et al. Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. *Biochemical pharmacology*. 1996;52(12):1855–1865. [PubMed: 8951344]
13. Ma BB, Hui EP, Wong SC, et al. Multicenter phase II study of gemcitabine and oxaliplatin in advanced nasopharyngeal carcinoma--correlation with excision repair cross-complementing-1 polymorphisms. *AnnOncol*. 2009;20(11):1854–1859.
14. Chia WK, Teo M, Wang WW, et al. Adoptive T-cell transfer and chemotherapy in the first-line treatment of metastatic and/or locally recurrent nasopharyngeal carcinoma. *MolTher*. 2014;22(1):132–139.
15. Louis CU, Straathof K, Bollard CM, et al. Adoptive transfer of EBV-specific T cells results in sustained clinical responses in patients with locoregional nasopharyngeal carcinoma. *JImmunother*. 2010;33(9):983–990. [PubMed: 20948438]
16. Hsu C, Lee SH, Ejadi S, et al. Safety and Antitumor Activity of Pembrolizumab in Patients With Programmed Death-Ligand 1-Positive Nasopharyngeal Carcinoma: Results of the KEYNOTE-028 Study. *J Clin Oncol*. 2017;35(36):4050–4056. [PubMed: 28837405]
17. Ma BBY, Lim WT, Goh BC, et al. Antitumor Activity of Nivolumab in Recurrent and Metastatic Nasopharyngeal Carcinoma: An International, Multicenter Study of the Mayo Clinic Phase 2 Consortium (NCI-9742). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2018;Jco2017770388.

Figure 1.
Event free survival (EFS) and overall survival (OS) after first salvage chemotherapy.

TABLE 1.

Treatment and outcomes after first salvage therapy

Patient	Age at 1 st relapse (years)	Site(s) of 1 st relapse	1 st salvage regimen	EFS after 1 st relapse (months)	OS after 1 st relapse (months)
1	16	Bone/Soft Tissue	Gem/Ox	20 [*]	20 ^{**}
2	17	Bilateral Lung/Liver	Ox/Dox	76 [*]	76 ^{**}
3	11	Lung	Carbo/Gem/Pacli	7	11
4	16	Bone	Carbo/Gem/Pacli	7	22
5	15	Bone/Muscle/Nodes	Carbo/Doce/XRT	4	14
6	18	Bone/Lung/Nodes	Carbo/5FU/Doce/XRT	15	22
7	18	Bone	Carbo/Pacli/Ifos/XRT/EBVST	43 [*]	43 ^{**}
8	15	Lung/Eyes	Carbo/Pacli/XRT	3	32 ^{**}
9	17	Nasopharynx	Carbo/Pacli	3	56 ^{**}
10	11	Bone	Excision/Dox/VCR/Cyclo/Irino/EBVST	49 [*]	49 ^{**}
11	13	Lung	Nivolumab	12 [*]	12 ^{**}
12	16	Bone	Gem/Vino	2	13
13	18	Cervical Nodes	Cetuximab/XRT	7	21
14	12	Bone	Irino/Topo	3	17

EFS, event free survival; OS, overall survival; Gem, gemcitabine; Ox, oxaliplatin; Dox, doxorubicin; Carbo, carboplatin; Pacli, paclitaxel; Doce, docetaxel; XRT, radiation therapy; 5FU, 5-fluorouracil; Ifos, ifosfamide; EBVST, Epstein-Barr virus-specific T lymphocytes; VCR, vincristine; Cyclo, cyclophosphamide; Irino, irinotecan; Vino, vinorelbine; Topo, topotecan.

* Continued remission at time of study completion.

** Patient alive at time of study completion.