Original Study

Comparative Study of L-Asparaginase-Based LOP Regimen Over CHOP Regimen Before Radiotherapy for Stage IIE Extranodal Nasal Type NK/T Cell Lymphoma: A Study of 2 Centers

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Abstract

At present, various L-asparaginase-based regimens have been used to treat stage IIE extranodal nasal type Natural Killer (NK)/T cell lymphoma. In this retrospective study we analyzed the data of 80 patients to evaluate the efficacy of a new L-asparaginase-based LOP (L-asparaginase, vincristine, and dexamethasone) regimen with radiotherapy (RT) protocol over classic CHOP (cyclophosphamide, tetrahydropyanyl adriamycin, vincristine and prednisone) with RT protocol in the Guizhou province of China. Results showed that the protocol is a safe alternative compared with other protocols reported in the literature.

Background: In this study we evaluated the efficacy of an L-asparaginase-based LOP (L-asparaginase, vincristine, and dexamethasone) regimen in extranodal Natural Killer (NK)/T-cell lymphoma (ENKTL) patients in the Guizhou province of China. **Patients and Methods:** Forty-eight patients were treated with the LOP (L-asparaginase, vincristine and dexamethasone) regimen chemotherapy (CT) and 32 patients with the CHOP (cyclophosphamide, tetrahydropyanyl adriamycin, vincristine, and prednisone) regimen. These patients then received involved-field radiotherapy (RT) with the doses of DT = 49-59 Gy. **Results:** A significant improvement of clinical end points with the LOP regimen was noticed compared with the CHOP regimen: 33 (68.8%) versus 16 (50.0%) for complete responses; 10 (20.8%) versus 5 (15.6%) for partial responses. There were statistical differences in objective response rates (43 [89.6%] for LOP vs. 21 [65.6%] for CHOP; $P = .009$), 3 years of overall survival (42 [87.5%] for LOP vs. 20 [62.5%] for CHOP; $P = .006$) and progression-free survival (32 [79.2%] for LOP vs. 16 [50.0%] for CHOP; $P = .007$). **Conclusion:** The results showed that the LOP regimen is safe and much more efficient than the CHOP regimen for stage IIE ENKTL patients. They indicate that the LOP regimen is a satisfying alternative protocol among the other L-asparaginase-based regimens reported so far, such as SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide), GELOX (gemcitabine, oxaliplatin, and L-asparaginase), CHOP-L, and sandwich (CT, then RT, then CT).

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Introduction

Extranodal Natural Killer (NK)/T-cell lymphoma (ENKTL), nasal type is an Epstein-Barre virus infection-associated non-Hodgkin lymphoma and occurs frequently in Asia and in Native Americans in parts of central and South America. It begins typically as lethal midline granuloma, progressively invading the nasal cavity, nasopharynx, palate, and causes facial destruction with distant skin and soft tissue metastasis.[1,2] Histologically, these neoplastic cells

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express cytoplasmic CD3ε, CD56, and cytotoxic markers (granzyme B, perforin, TIA-1), but negative for surface CD3, CD5, or TCR. ENKTL in early-stage is very sensitive to radiotherapy (RT).[3] RT is an important treatment for ENKTL and cumulated clinic data showed that early or upfront RT is essential for good local control. The dose of RT is an important parameter and it is routinely recommended to treat ENKTL with high doses of RT (50-54 Gy) to achieve a favorable local control rate.[4-6] Whether higher doses would achieve better local control rates remains unresolved.

Extranodal NK/T-cell lymphoma is an aggressive non-Hodgkin lymphoma. Although more than half of the patients are diagnosed as having localized disease, the overall prognosis is poor. Chemotherapy (CT), such as the adriamycin-based CHOP (cyclophosphamide, tetrahydropyanyl adriamycin, vincristine and prednisone) regimen, has been introduced into the treatment for early-stage I/II ENKTL in addition to RT and has substantially improved the clinical outcome of patients with ENKTL.[7-12] ENKTL in advanced-stage develops resistance to CT, and relapse occurs in approximately 40% of the patients, probably because of the expression of P-gp multiresistance protein and the prognosis is poor.[13,14] The complete response (CR) rate for CHOP-like CT alone has been shown to be $< 40\%$, with a 5-year failure-free survival ranging from 25% to 40%.[15] The major improvement in ENKTL treatment was made when L-asparaginase, which devoids lymphoblasts of L-asparagine, was introduced into clinical use.[16-19] L-asparaginase hydrolyzes serum asparagine and deprives some tumor cells of the required amino acid. That process results in rapid inhibition of protein synthesis and delayed inhibition of DNA and RNA synthesis to yield anticancer effects in certain tumor cells, especially in lymphocytes that lack L-asparagine synthetase. Clinical study showed that L-asparaginase-based CT is effective for early-stage as well as advanced/relapsed/refractory ENKTL.[20-25] At present, the modality of CT with RT for early stage ENKTL has been widely accepted in clinical practice, however, a further effort is still made to determine the optimal CT protocol for early-stage ENKTL, because a variety of drug regimens have been proposed, such as SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) and GELOX (gemcitabine, oxaliplatin, and L-asparaginase).[21,26-28] In addition, recent clinical reports suggest the advantage of giving RT before CT for early-stage ENKTL[29] and the use of the "sandwich" protocol (CT then RT then CT).[25]

This retrospective study presents the data of 80 patients who has been diagnosed as stage II ENKTL according to the World Health Organization (WHO) classification,[30,31] and received either the CHOP regimen treatment or the L-asparaginase-based LOP (L-asparaginase, vincristine, and dexamethasone) regimen treatment before RT. The patients had been followed-up for a median 39 months and the clinical benefits and side effects were analyzed.

Patients and Methods

Patients: Eligibility Criteria

In total, 127 patients from Guizhou cancer hospital and Guizhou provincial people's hospital were registered from March 2008 to July 2015 and the patients were required to have a biopsy-proven diagnosis of nasal ENKTL and be at least 18 years old. The eligibility criteria for inclusion in this study were as follows: (1) diagnosed ENKTL with typical morphology and immunophenotype according to the WHO classification of lymphomas; (2) primary site localized in the nasal cavity; (3) Ann Arbor stage IIE disease; (4) no previous therapy for ENKTL; (5) an Eastern Cooperative Oncology Group (ECOG) status of 0-2; (6) acceptance of the CHOP or LOP CT regimen with RT. The exclusion criteria were previous or concomitant malignant tumors and any coexisting study protocol. The ENKTL patients with non-nasal sites, such as skin or gastrointestinal tract, were excluded even if tumors were localized. In total, 80 patients formed the population of this study.

The patients underwent clinical staging with history and physical examination, chest radiography, serum biochemistry, magnetic resonance imaging, and/or computed tomography scans of the head and neck, computed tomography of the chest, abdomen, and pelvis, and bone marrow examination. All of the patients gave their written informed consent and this retrospective study was approved by the institutional review boards of the 2 hospitals.

Treatment Method

Thirty-two patients received the CHOP regimen (cyclophosphamide 750 mg/m^2 given intravenously on day 1; hydroxydaunorubicin 50 mg/m^2 given intravenously on day 1; vincristine 1.4 mg/m^2 but no more than 2 mg given intravenously on day 1; prednisolone 60 mg/m^2 given orally on days 1-5) with involved-field RT. Forty-eight patients received the LOP regimen (L-asparaginase 6000 IU/m^2 given intravenously on days 1, 3, 5, 7, 9, 11, and 13; vincristine 1.4 mg/m^2 but no more than 2 mg given intravenously on days 1 and 8; dexamethasone 10 mg given intravenously on days 1 to 7) with RT. Before the administration of L-asparaginase, an intradermal skin test was performed with 50 IU L-asparaginase dissolved in 1 mL normal saline. After 1 hour, if no obvious rash, erythema, pruritus, or other allergic reaction occurred, the patients received intravenous 6000 IU/m^2 L-asparaginase. Seven patients had experienced hypersensitivity to L-asparaginase and received the homology pegaspargase (2500 IU/m^2 given intramuscularly on day 1). Both CT cycles were repeated at 21-day intervals. All drugs were administered only if the absolute neutrophil count was $> 1.5 \times 10^9$/L and the platelet count was $> 75 \times 10^9$/L before each cycle. If either the neutrophils or platelets were lower than these levels, treatment was delayed for 3 to 7 days.

Involved-field radiation therapy began 3 weeks after completion of the fourth cycle of CT. The radiation range included ethmoid sinus, ipsilateral maxillary sinus, sphenoid sinus, nasopharynx, and nasal cavity, and was decided by the invasive range. All patients received bilateral neck irradiation. Radiation dose was essentially adjusted to tumor burden. The total RT dose of 49-59 Gy was administered once a day, 5 fractions every week over approximately 5 weeks according to a conventional fraction schedule to 27-32 fractions according to pre-CT gross disease extent. Clinical target volume (CTV) included gross tumor volume with a margin of at least 20 mm and the entire nasal cavity and parasinuses. Planning target volume (PTV) included CTV with a 5-mm margin. For all of the patients, CTV and PTV also included the involved cervical lymph node area. RT was postponed until the toxicity was reduced to Grade 2 if one or more of the following adverse events were observed: Grade 4 leukopenia or neutropenia, platelet count $< 25 \times 10^9$/L, any Grade 3 nonhematologic toxicities except for