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Clinical Outcomes and Prognostic Factors of Up-Front Autologous Stem Cell Transplantation in Patients with Extranodal Natural Killer/T Cell Lymphoma

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A B S T R A C T

Limited data exist on up-front autologous stem cell transplantation (ASCT) in extranodal natural killer/T cell lymphoma (ENKTL). Sixty-two patients (43 men and 19 women) with newly diagnosed ENKTL who underwent up-front ASCT after primary therapy were identified. Poor-risk characteristics included advanced stage (50%), high-intermediate to high-risk International Prognostic Index (25.8%), and group 3 to 4 of NK/T Cell Lymphoma Prognostic Index (NKPI, 67.7%). Pretransplant responses included complete remission in 61.3% and partial remission in 38.7% of patients, and final post-transplantation response included complete remission in 78.3%. Early progression occurred in 12.9%. At a median follow-up of 43.3 months (range, 3.7 to 114.6), 3-year progression-free survival (PFS) was 52.4% and 3-year overall survival (OS) was 60.0%. Patients with limited disease had significantly better 3-year PFS (64.5% versus 40.1%, $P = .017$) and OS (67.6% versus 52.3%, $P = .048$) than those with advanced disease. Multivariate analysis showed NKPI and pretransplant response were independent prognostic factors influencing survival, particularly NKPI in limited disease and pretransplant response in advanced disease. Radiotherapy was an independent factor for reduced progression and survival in patients with limited disease, but anthracycline-based chemotherapy was a poor prognostic factor for progression in patients with advanced disease. Up-front ASCT is an active treatment in ENKTL patients responding to primary therapy.

INTRODUCTION

Extranodal natural killer/T cell lymphoma (ENKTL) is a distinct subtype of non-Hodgkin lymphoma that mainly involves nasal, paranasal, and oropharyngeal areas and is closely associated with Epstein-Barr virus (EBV) infection [1,2]. ENKTL is aggressive in nature and is frequently resistant to anthracycline-based chemotherapy [3]. Although ENKTL is more prevalent in East Asia than in Western countries, this disease is generally rare worldwide [4]. Because of the rarity of the disease and the consequent lack of prospective randomized trials, evidence-based standard therapy for ENKTL has not been established. Given the fact that ENKTL is radiosensitive disease [5,6], treatment strategies are mainly affected

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by the Ann Arbor stage at initial diagnosis (either limited [stage I or II] or advanced [stage III or IV] disease). Several more recent phase II studies in patients with limited disease suggested that combined chemotherapy–radiotherapy was associated with improvement of clinical outcomes [7-11]. In addition, a small phase II study in patients with advanced disease showed that a regimen of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) had a promising response rate and improved survival [12]. However, a substantial number of patients with ENKTL, especially those with advanced disease, eventually experience relapse after treatments. Moreover, once ENKTL recurs, prognosis is extremely dismal [13]. This suggests that further treatment strategies are needed to prevent relapse and improve the survival.

High-dose therapy with autologous stem cell transplantation (ASCT) can be an attractive option for the treatment of ENKTL as an up-front consolidation strategy [1]. However, the effectiveness of ASCT on patients with distinct risk factors, optimal transplant timing, and available prognostic parameters to predict better outcomes has not yet been determined in ENKTL. Most data regarding ASCT in ENKTL were derived from small case series, and interpretation was complicated by heterogeneous populations [14-19]. In fact, these studies included fewer than 20 cases with up-front ASCT, and results from these studies are therefore not readily applicable in up-front ASCT in ENKTL. It is likely that prospective trials are finally needed to examine the role of ASCT in the treatment of ENKTL. However, before treatment strategies for up-front ASCT in ENKTL can be evaluated prospectively, comprehensive analyses from retrospective data may provide valuable insight into feasibility, response and survival rates, clinical prognostic factors, and treatment failure patterns for up-front ASCT strategies. Therefore, the purpose of this study was to investigate clinical outcomes and available prognostic factors in patients with ENKTL treated by up-front ASCT after primary therapy. These analyses may provide basic data for designing future prospective trials.

METHODS

Patient Population and Diagnostic Evaluation

Patients were recruited from 9 institutions belonging to the Consortium for Improving Survival of Lymphoma of the Korean Society of Hematology Lymphoma Working Party. Patients were eligible for inclusion in the study if they had received a diagnosis of ENKTL and underwent up-front ASCT after primary therapy between January 2004 and December 2013. Diagnoses of all patients included in this analysis were pathologically confirmed by tumor tissues obtained from the site of the disease, which were based on typical histologic features: positive immunohistochemical expression of cytoplasmic CD3, CD56, and cytotoxic molecules and positive EBV in situ hybridization results [20]. Patients were excluded if they had been diagnosed with aggressive NK cell leukemia. Patients who underwent salvage ASCT after disease progression were also excluded.

In all patients complete staging procedures, including medical history, physical examination, complete blood count, serum biochemistry with lactate dehydrogenase, computed tomography (CT) scan or magnetic resonance imaging scan of the involved region, CT scan of chest and abdomen, and bilateral bone marrow trephination biopsies, were performed. Baseline positron emission tomography (PET)-CT scan was performed at the discretion of the physicians based on their institution's policy. Using the results of these staging procedures, patients were classified into 2 groups: limited disease and advanced disease groups. The limited disease group included patients with stage I or II disease and the advanced disease group included patients with stage III or IV disease. Prognosis was determined according to the International Prognostic Index and the NK/T Cell Lymphoma Prognostic Index (NKPI) [21].

Based on the site of primary tumor, ENKTL cases were divided into 2 groups: the upper aerodigestive tract NK/T cell lymphoma (UNKTL) and extra-upper aerodigestive tract NK/T cell lymphoma (EUNKTL) groups [22]. In brief, UNKTL was defined as that involving the nasal cavity, nasopharynx, and upper aerodigestive tract, whereas EUNKTL was defined as the presence of primary tumors at other regions in the absence of nasal disease. All patients provided written informed consent in accordance with institutional guidelines, and the study protocol was reviewed and approved by the institutional review board at each participating institution.

Initial Treatment and Response Evaluation

Initial primary therapy consisted of the following treatment modalities: anthracycline-based primary chemotherapy with or without involved-field radiotherapy (IFRT), non–anthracycline-based chemotherapy with or without IFRT, and concurrent chemoradiotherapy with cisplatin followed by non–anthracycline-based chemotherapy. The anthracycline-based chemotherapeutic regimens used were cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone. Non–anthracycline-based chemotherapeutic regimens included SMILE; etoposide, ifosfamide, dexamethasone, and L-asparaginase (VIDL); ifosfamide, methotrexate, etoposide, prednisone plus L-asparaginase (IMEP plus L-asp); and etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD). In patients with limited disease, IFRT was administered after the completion of chemotherapy at the discretion of the treating physician. Concurrent chemoradiotherapy consisted of radiation therapy with a total dose of 36 to 44 Gy in 18 to 22 fractions and weekly administration of 30 mg/m^2 cisplatin for 4 weeks.

According to primary chemotherapy, patients were categorized into 2 groups: anthracycline-based chemotherapy and non–anthracycline-based chemotherapy groups (regardless of the sequence of chemotherapy and [chemo]radiotherapy). Patients generally proceeded to ASCT when they completed preplanned cycles of chemotherapy and achieved objective response. However, patients could proceed to ASCT if they had significant regimen-related toxicities or reasons other than disease progression to discontinue chemotherapy, which was at the discretion of the physician.

Tumor responses were assessed using the revised International Working Group criteria [23]. If PET-CT was performed, the response of PET-CT was assessed according to rules proposed by the International Harmonization Project in lymphoma [24]. Pretransplant response was assessed within 4 weeks before conditioning chemotherapy was administered, and response to ASCT was assessed 2 to 3 months after transplantation.

Stem Cell Mobilization and High-Dose Therapy with ASCT Procedure

Stem cell mobilization for ASCT was performed according to published recommendations [25]. Conditioning chemotherapy consisted of total body irradiation (TBI)–based and non–TBI-based regimens. The TBI-based regimen was etoposide, cyclophosphamide, and fractionated TBI [19], whereas non–TBI-based regimens included busulfan, cyclophosphamide, and etoposide; busulfan, melphalan, and etoposide; busulfan, etoposide, cytarabine, and melphalan; carmustine, etoposide, cytarabine, and melphalan; and busulfan and thiotepa.

Statistical Analysis

The primary endpoints were progression-free survival (PFS) and overall survival (OS) after ASCT. Survival endpoints were calculated from the date of ASCT until progression, death, or last follow-up, as appropriate. PFS and OS were estimated using the Kaplan-Meier method. Clinical variables were compared using Pearson's chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. Differences in PFS and OS among comparison groups were tested using a log-rank test in univariate analyses. Multivariate analysis was carried out using Cox proportional hazards models. Variables with $P < .10$ in univariate analyses were included in the multivariate model. The results were reported with a hazard ratio (HR) and 95% confidence interval (CI). $P < .05$ was considered to reflect statistical significance. All statistical analyses were performed using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient Cohort

From 2004 to 2013, 66 patients with ENKTL who underwent up-front ASCT were recruited. Of these 66 patients, 4 did not meet the entry criteria: 2 patients were initially diagnosed with aggressive NK cell leukemia and 2 patients underwent ASCT after salvage chemotherapy. In total, 62 patients were registered for this analysis.