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Quantifying Benefit of Autologous Transplantation for Relapsed Follicular Lymphoma Patients via Instrumental Variable Analysis

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A B S T R A C T

The role of autologous stem cell transplantation (ASCT) in patients with relapsed follicular lymphoma (FL) remains controversial because of a lack of proven overall survival (OS) benefit versus nontransplant strategies. We conducted a comparative effectiveness research study involving 3 tertiary Canadian cancer centers to determine whether the ASCT-based approach used at 1 center improved OS relative to non-ASCT approaches used at the other centers. Of 1082 consecutive patients aged 18 to 60 years and diagnosed with FL from 2001 to 2010, the study population included 355 patients who experienced relapse from chemotherapy (center A = 96, center B = 84, center C = 175). Data were analyzed according to the instrumental variable of treatment center to control for confounding factors. The frequency of using ASCT at first or second relapse was significantly different between the centers (A = 58%, B = 7%, C = 5%, $P < .001$). With a median follow-up of 69.1 months, the actuarial 5-year OS rates after first chemotherapy relapse were 89%, 60%, and 60% for centers A, B, and C respectively (log rank $P < .0001$). Based on instrumental variable analysis, the use of ASCT at relapse 1 or 2 significantly decreased the risk of death from first relapse (HR .127, $P = .004$) and from initial diagnosis (HR .116, $P = .004$). In conclusion, for FL patients who relapse after chemotherapy, these results strongly support more frequent use of ASCT at first or second relapse.

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INTRODUCTION

Follicular lymphoma (FL) represents approximately 25% of all lymphomas seen in North America [1,2]. The initial treatment of symptomatic advanced FL is guided by numerous, well-designed, large, prospective randomized controlled trials (RCTs) [3-7]. Management of relapsed FL, however, is highly controversial, because of a paucity of RCTs. Therapy options range from palliative-intent single-agent therapy to curative-intent high-dose therapy and autologous stem cell transplantation (ASCT) or allogeneic hematopoietic stem cell transplantation (alloSCT).

Despite reports of very lengthy progression-free survival after ASCT and alloSCT [8-12], the role of high-dose therapy for FL remains unclear, and its use varies widely depending on physician and treatment center. Available data supporting the use of high-dose therapy for relapsed FL are mainly from retrospective studies and are influenced by selection bias [13-16]. Although RCTs remain the gold standard for clinical research, they are associated with high cost, long duration, idealized conditions not generalizable to real-world practice, and limited ability to detect overall survival (OS) benefit due to cross-over of control arm patients to ASCT at subsequent relapse. These factors, plus enrollment issues related to strong physician and patient treatment preferences, limit the feasibility of completing an RCT to evaluate OS benefit of ASCT for relapsed FL. This was evident in the only published phase III trial suggesting benefit of ASCT for relapsed FL, which failed to meet accrual targets [17]. In addition to the lack of prospective RCTs, there are insufficient

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population-based data to estimate the proportion of eligible relapsed FL patients who currently receive ASCT or their OS relative to relapsed FL patients treated with other strategies.

Only a few centers across Canada routinely offer ASCT for relapsed FL, including only 1 of the 3 tertiary university-based cancer centers in Western Canada. The objective of this study was to determine whether ASCT improves OS for patients with relapsed FL at these 3 Western Canadian cancer centers through use of instrumental variable analysis (IVA) [18-21] in which the instrumental variable was "treatment center." An IVA is a statistical method used to control for confounding and measurement error in observational studies, allowing for the possibility of making causal inferences with observational data because the IVA can adjust for both observed and unobserved confounding effects [18-21].

METHODS

Patients

The Alberta Cancer Registry (for the Tom Baker Cancer Centre, Calgary and Cross Cancer Institute, Edmonton) and the British Columbia Cancer Agency (Vancouver) Lymphoid Cancer Database were interrogated to identify all patients aged 18 to 60 years who were diagnosed with FL between 2001 and 2010 and who relapsed after an initial course of chemotherapy or chemoimmunotherapy and required second-line therapeutic intervention. Patients who presented with grade 3B FL or with concurrent diffuse large B cell lymphoma were excluded, but those who developed transformation after diagnosis were included. Patients who relapsed after rituximab monotherapy, but no cytotoxic chemotherapy, were excluded. Once data collection was complete, the de-identified datasets were combined for analysis at the Tom Baker Cancer Centre, Calgary. The study was approved by the Alberta and British Columbia Cancer Agency Research Ethics Boards. Outcomes for 32 patients receiving ASCT at center A were previously reported [9].

Statistical Analysis

The Kruskal-Wallis test was applied to compare continuous variables, and Fisher's exact test was used to compare categorical variables. The primary endpoint of the study was OS, defined as the time from first chemotherapy relapse to last follow-up or death from any cause. OS was estimated using the Kaplan-Meier method, and differences between treatment centers were compared using the log-rank test. Univariate Cox proportional hazard method was used to determine the factors associated with OS. Variables significant at the univariate level ($P < .1$) were selected for multivariate Cox proportional hazard regression model analyses with a backward stepwise procedure. A 2-sided $P < .05$ was used for all statistical significance. SAS version 9.4 (SAS Institute Inc., Cary, NC) and R Software version 3.1.2 (R Core Team 2015, R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org) were used for statistical analyses.

With knowledge that treatment center would be associated with the use of ASCT at relapse 1 or 2 but otherwise should not be associated with OS, an IVA was used to evaluate the potential impact of ASCT on OS, in which the instrumental variable was "treatment center." The IVA method was based on 2-stage residual inclusion estimation [22,23]. This approach initially performs logistic regression for ASCT use on the IV (treatment center) and other variables and then calculates residuals based on this logistic model. The second step includes use of ASCT, other variables, and the estimated residuals into a Cox regression model.

RESULTS

Patient Characteristics

The Alberta Cancer Registry identified 539 patients (in centers A and B) and the British Columbia Lymphoma Database identified 543 patients (center C), aged 18 to 60 years, who were diagnosed with FL between 2001 and 2010. Of these 1082 patients, 355 experienced relapse after an initial course of chemotherapy and met eligibility for inclusion in the study (center A = 96, center B = 84, center C = 175). Frequency of baseline characteristics at diagnosis, including male gender, advanced stage, elevated lactate dehydrogenase and hemoglobin < 120 g/L, were similar across the 3 centers. Follicular Lymphoma International Prognostic Index (FLIPI) score distribution was not different between centers A and B ($P = .12$). Center C did not record this information. Patient characteristics at first chemotherapy relapse were not different between centers, although some variables were missing from center C.

Outcome Analysis

Characteristics of 355 study patients who relapsed postchemotherapy

Table 1 lists patient characteristics at initial diagnosis and at first relapse for the 355 study patients. The largest treatment difference between centers A, B, and C was the frequency of ever using ASCT ($P < .001$) and the use of ASCT in first or second relapse postchemotherapy (A = 58%, B = 7%, C = 5%, $P < .001$). As previously reported [9] center A predominantly uses melphalan 180 mg/m^2 day −1 and total body irradiation 500 cGy day 0 conditioning for relapsed FL and conventional BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning for transformed disease. Centers B and C use BEAM conditioning with ASCT for FL or transformed lymphoma. The source of stem cells was peripheral blood for all centers, and no ex vivo purging was performed.

Factors associated with greater use of ASCT in first or second relapse included relapse after front-line rituximab (R)-chemotherapy + R-maintenance ($P = .01$) and the use of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with front-line therapy ($P < .001$). On the other hand, the use of fludarabine ($P < .001$), alloSCT ($P = .05$), and not using R-chemotherapy after relapse ($P < .001$) were associated with less frequent use of ASCT in first or second relapse. Factors not associated with the use of ASCT in first or second relapse included ever transformation ($P = .23$), initial time to progression <1 year ($P = .12$), age >60 years at relapse ($P = .29$), ever R-maintenance ($P = .06$), and elevated lactate dehydrogenase ($P = .55$). Of patients who received ASCT, 12 of 59 patients (20%) from center A, 6 of 15 (40%) from center B, and all 12 patients (100%) from center C were determined to have clinical or pathologic transformation before ASCT. No ASCT patients developed myelodysplastic syndrome or acute myeloid leukemia.

Outcomes of 355 study patients who relapsed postchemotherapy

At the time of analysis, the median follow-up of surviving patients from diagnosis was 108.8 months (range, 8.6 to 162.3) and from first chemotherapy relapse 69.1 months (range, .1 to 151.8). The median follow-up times were similar for centers A, B, and C from diagnosis and from first chemotherapy relapse.

Factors significantly associated with shorter OS after first chemotherapy relapse in univariate analysis are listed in Table 2. In contrast, grade 3A FL ($P = .50$), advanced stage ($P = .62$), initial treatment with watchful waiting or radiotherapy ($P = .76$), type of initial chemotherapy (CHOP, fludarabine, or other), age > 60 years at relapse ($P = .89$), ever alloSCT ($P = .80$), and ever doxorubicin after relapse ($P = .06$) were not predictive of OS from first chemotherapy relapse. The relationship between OS after first chemotherapy relapse and treatment center is illustrated in Figure 1 and between OS after relapse and the use of ASCT in Figure 2. The actuarial 5-year OS rates after first chemotherapy relapse were 88.9%, 60.0%, and 59.8% for centers A, B, and C, respectively (log rank $P < .0001$). The actuarial 5-year OS rates after first chemotherapy relapse for patients treated with ASCT at first or second relapse, never treated with ASCT,

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