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CORRESPONDENCE

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Late infections and secondary malignancies after bendamustine/rituximab or RCHOP/RCVP chemotherapy for B-cell lymphomas

To the Editor:

First-line treatment of indolent B-cell lymphomas (including follicular [FL], marginal zone [MZL], lymphoplasmacytic [LPL]), and mantle-cell lymphoma (MCL) has undergone a shift after two randomized trials (the Study group indolent Lymphomas [StiL], and the BRIGHT trial) demonstrated noninferiority of bendamustine-rituximab (BR) compared with RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or RCVP (rituximab, cyclophosphamide, vincristine, and prednisone) chemotherapy.[1,2] However, updates of these trials, as well as some observational data,[3] raised questions about potentially increased risk of secondary malignancies (SM) and late infections after BR. Flinn et al. reported that BR (compared with RCHOP/RCVP) was associated with more profound lymphocytopenia, a significantly higher rate of SM (19% versus 11%, $P = .022$), and a numerically higher mortality from infections, particularly pneumonias.[4] In contrast, no difference in SM between BR or RCHOP (17% and 20%, respectively) was reported in the StiL trial. Furthermore, in the GALLIUM study, which randomized FL patients to rituximab or obinutuzumab in combination with bendamustine or CHOP/CVP, patients receiving bendamustine experienced decreased T-cell counts, more fatal adverse events (5% versus 2%), grade 3–4 infections (23% versus 12%), and SM (9% versus 4%), particularly during postinduction maintenance therapy.[5] Our objective was to examine the incidence of hospitalizations, infections, and SM among patients treated with BR or RCHOP/RCVP using population-based data from the US Surveillance, Epidemiology, and End Results (SEER-Medicare) registry. The registry contains clinical records of cancer cases reported from geographical areas covering about 28% of the US population, linked to Medicare claims for health services, including administration of chemotherapy and all hospitalizations. The study was approved by the Institutional Review Board at Rhode Island Hospital.

We identified Medicare beneficiaries older than 65 years at diagnosis, who received first-line chemotherapy for FL (excluding grade 3), MZL, LPL, or MCL in 2009–2013, and had complete Medicare claims available. BR or RCHOP/RCVP-like regimens were ascertained using codes for specific drugs recorded within 15 days from the start of chemotherapy.[6] Because recurrences of lymphoma, indications to discontinue or restart chemotherapy cannot be derived from Medicare data, we did not distinguish patients receiving maintenance rituximab. We calculated incidence rates (IR) for 3 endpoints of interest: any hospitalization, hospitalization with an infection, or hospitalization with a pneumonia, in sequential 6-month periods after the start of chemotherapy. Infections and pneumonias were identified according to the Agency for Healthcare Research and Quality Clinical Classifications Software (http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp). We then compared incidence in proportional hazard models adjusting for patients' age, sex, race, marital status, record of prior malignancies, Medicaid eligibility (an indicator of individual poverty), reason for Medicare enrollment (age or disability), prevalent poverty in the census tract of residence, baseline health (Charlson comorbidity index, claims-based performance status indicator, and hospitalization within a year before chemotherapy), lymphoma histology, stage, time from diagnosis to treatment, and calendar year. We identified SM (defined as all nonlymphoid cancers reported for a given patient, and diagnosed >6 months from the start of chemotherapy) and compared their cumulative incidence in a competing-risk model accounting for the risk of death, and adjusting for age, sex, race, and type of lymphoma. All model estimates are reported with 95% confidence intervals (95%CI), with two-sided $P < .05$ considered statistically significant.

The analysis included 1791 patients treated with first-line BR ($N = 711$, 40%), RCHOP ($N = 530$, 29%), or RCVP ($N = 550$, 31%), whose median age was 75 years (range, 65–96). Patients' characteristics are detailed in Supporting Information Table S1. In the analytic cohort there were 43% women, 52% patients with FL, 27% with MCL, and 21% with MZL/LPL. Median time from diagnosis to first chemotherapy was 58 days (interquartile range 39–95). The proportion receiving BR increased from 4% in 2009 to 68% in 2013 (Supporting Information Figure S1A). Patients treated with BR were on average older ($P = .001$), and more often had MCL (31% versus 24%, $P = .003$), but there were no significant differences in performance status, comorbidities, or time from diagnosis to treatment between BR and RCHOP/RCVP groups.

The incidence of hospitalizations, infections, and pneumonias was lower for BR during the first 6 months of observation (Supporting Information Figure S1B-D). Subsequently, the incidence decreased slower for BR than for RCHOP/RCVP, and consequently patients receiving BR experienced 27% higher risk of hospitalization, 54% higher risk of infections, and 93% higher risk of pneumonia throughout the 2nd year of follow-up (Table 1). The absolute increase in incidence was very small: IR difference during the second year of follow-up was 0.9 per 100 person-months for hospitalizations (95%CI, 0.2-1.6), 0.9 for infections (95%CI, 0.5-1.4), and 0.6 for pneumonia (95%CI, 0.3-1.0).

TABLE 1 Comparison of incidence of all hospitalizations, and hospitalizations with a diagnosis of infection or pneumonia, among Medicare beneficiaries treated with bendamustine-rituximab (BR) or RCHOP/RCVP chemotherapy

	Hospitalization[a]			Infection[a]			Pneumonia[a]		
Time from chemotherapy	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
BR vs. RCHOP/RCVP									
0–12 months	0.81	0.73-0.91	.0003	0.87	0.74-1.02	.08	0.85	0.67-1.09	.20
12–24 months	1.27	1.07-1.51	.007	1.54	1.19-2.00	.0012	1.93	1.31-2.86	.001
24–36 months	0.99	0.80-1.22	.89	0.99	0.71-1.37	.94	0.81	0.48-1.38	.44
BR vs. RCHOP									
0–12 months	0.70	0.61-0.80	<.001	0.72	0.60-0.86	.0003	0.74	0.56-0.99	.04
12–24 months	1.05	0.86-1.29	.61	1.32	0.97-1.81	.07	1.58	0.99-2.53	.06
24–36 months	0.83	0.65-1.06	.13	0.79	0.54-1.14	.21	0.60	0.32-1.12	.11
BR vs. RCVP									
0–12 months	1.02	0.88-1.19	.75	1.14	0.91-1.41	.24	0.92	0.67-1.28	.63
12–24 months	1.49	1.19-1.88	.0007	1.79	1.26-2.53	.001	2.10	1.20-3.67	.009
24–36 months	1.19	0.91-1.55	.20	1.31	0.86-1.99	.20	1.11	0.57-2.15	0.76

[a]Based on Medicare claims for inpatient admissions.
CI: confidence interval; BR: bendamustine and rituximab; HR: hazard ratio; RCHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RCVP: rituximab, cyclophosphamide, vincristine, and prednisone.
The incidence was compared in proportional hazard models including patients treated with BR versus RCHOP/RCVP ($N = 1791$), BR versus RCHOP only ($N = 1241$), or BR versus RCVP only ($N = 1080$). All models adjusted for age, sex, race, marital status, history of prior malignancy, socio-economic status, comorbidity and performance status indicators, histology and stage of the lymphoma, time from diagnosis to initiation of chemotherapy, and calendar year.

The differences disappeared in the third year of follow-up, and were not statistically significant when BR was compared with RCHOP only.

With a median follow-up of 2.8 years and total observation time of 3779 person-years, 95 nonlymphoid SMs were observed, in 4% of patients receiving BR, and 6% of those receiving RCHOP/RCVP (Supporting Information Figure S1E). A majority of SMs were carcinomas, with <10 secondary myeloid malignancies. In a multivariable model we found no significant difference in the cumulative incidence of SM between patients treated with BR or RCHOP/RCVP (subhazard ratio, 1.13; 95%CI, 0.73-1.74; $P = .60$).

In this population-based cohort of patients who by virtue of their age were prone to cancers and opportunistic infections, we found only a slight absolute increase in the infectious risk during the second year after BR, compared with RCHOP/RCVP, and no discernible difference in SM. We acknowledge that the latter finding will require future reassessment due to short median follow up. These results, derived from the real-world practice, can reassure hematologists about the general safety of BR in older patients with lymphoma, although they highlight need for vigilance for infections during follow-up. Because many patients with indolent B-cell lymphomas experience prolonged survival, they should continue clinical surveillance for late infectious toxicities and age-appropriate screening for SM. Future research can help clarify whether the combination of bendamustine with obinutuzumab, or maintenance therapy with anti-CD20 antibodies may contribute to late infectious toxicity, as suggested by the GALLIUM study.[5] Cautious monitoring for late toxicities should be also implemented in trials which introduce lenalidomide maintenance after bendamustine-based induction therapy.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Urological complications associated with adult allogeneic stem cell transplantation

To the Editor:

Every year 50 000 patients receive stem cell transplantation worldwide, but data are lacking about urological complications associated with this therapy. Most studies were performed in paediatric stem cell transplantation or are retrospective analyses with a small number of cases. The complications mentioned were mostly urological infections and haematuria.[1] Another complication that arises under this therapy is the BK polyomavirus associated hemorrhagic cystitis (BKHC), which can occur in 5%-60% of the cases.[2] Other viruses which can lead to cystitis or even hemorrhagic cystitis following allogeneic stem cell transplantation are polyomavirus JC and uropathogenic adenoviruses.[3]

Since urological complications can cause severe problems with increased morbidity and rarely mortality, further investigations are needed.[4]

We conducted a prospective, single-center, noninterventional trial on urological complications assopciated with first adult allogeneic stem cell transplantation with a follow up time of one year after inpatient treatment. To our knowledge this is the first prospective study about urological complications under this therapy worldwide.

The inclusion criteria were patient over 18 years receiving their first allogeneic stem cell transplantation due to hematological disease. The use of low dose alemtuzumab (10 mg at day −2; respectively 20 mg in case of mismatch) for Graft versus host disease (GvHD) prophylaxis was mandatory. No exclusion criteria were defined. From November 2013 until December 2015 we were able to include 40 patients in our study. Statistical calculations were made by using SPSS 23.0 (SPSS Inc., Chicago, Ill., USA). All reported *P*-values were based on a two-sided hypothesis, $P < .05$ was considered to be significant.

Between November 2013 and December 2015, we were able to include 40 adult patients with a mean age of 52.8 years. Twenty seven (67.5%) of these patients were male and 13 (32.5%) were female. Acute myeloid leukemia (AML) was the most frequent underlying disease ($n = 15$; 37.5%). The majority of patients received intermediate intense conditioning protocols ($n = 31$; 77.5%).

On the whole, urological complications during inpatient treatment were quite common in this study population ($n = 26$; 65.5%). Acute renal failure ($n = 14$; 35.0%) and bacterial UTI ($n = 7$; 17.5%) were the most frequent complications. BKHC occurred only one time ($n = 1$; 2.5%). But viruria with absence of urogenital symptom and after infusion of the stem cell product occurred more often, e.g., BK viruria 11 (27.5%). Table 1 gives an overview of all urological complications and viruria during inpatient treatment. We did not observe adenoviruria after infusion of the stem cell product in this study population.

Additionally, we tested if BK viruria or JC viruria were associated with renal failure or acute GvHD, as previously reported. Interestingly, BK viruria was significantly associated with acute renal failure ($P = .007$; Fisher exact test). In this population, there was no significant association of BK and JC viruria with acute GvHD.

The main result of our study is that urological complications under this therapy are very common, (e.g., 65.5%) during inpatient treatment. On the whole, bacterial UTI and acute renal failure are the most frequent complications. BKHC only occurred one time in our study population which is clearly less than described in the literature.[2] One major risk factors for BKHC mentioned in other studies was myeloablative conditioning[5]; in our study population, a majority of patients were conditioned with an intermediate intense protocol. BK and JC viruria