

in RBC or platelet level is not evident, but the increase is resolved during follow-up. "Probable MPN" indicates that the increase in RBC or platelet level continues during follow-up. "Proven MPN" is diagnosed with PV or ET based on the WHO criteria. In total, 1,729 CI patients (1,003 men; 726 women) of median age 73 years (range, 19–96 yr) were reviewed. Thrombocytosis (platelets $\geq 450 \times 10^9/L$) was evident in 69 (4.0%) patients at diagnosis or during follow-up. Reactive thrombocytosis was the most common form of thrombocytosis (N=62, 3.6%). Three (0.2%) patients were considered to exhibit possible ET, and four (0.2%) had proven ET. The causes of reactive thrombocytosis (N=62 patients) included infection (N=59, 95.2%), bleeding (N=1, 1.6%), and iron-deficiency (N=1, 1.6%). Erythrocytosis was evident in 79 (4.6%) patients at diagnosis or during follow-up. Reactive erythrocytosis was the most common form of erythrocytosis (N=50, 2.9%), followed by possible PV (N=21, 1.2%), probable PV (N=6, 0.3%), and proven PV (N=2, 0.1%). None of the 27 patients with possible or probable PV underwent further investigations. Particularly, the *JAK2* mutational status was not explored. Reactive erythrocytosis (N=50) was detected during diagnosis and follow-up in 28 (56.0%) and 22 (44.0%) patients, respectively, and all cases were attributable to hemoconcentration. Of the four patients with proven ET, two lacked any other predisposing factor for thrombosis. All patients with proven ET and PV exhibited multifocal CI and previously undetected infarctions on CI diagnosis.

These results showed that many CI patients with erythrocytosis did not undergo further evaluation in terms of a PV diagnosis and that *JAK2* mutational status should be evaluated in such patients. Stroke is a global health problem with a global lifetime risk of approximately 25% in people 25 years and older (as of 2016). People living in East Asia, Central Europe, and Eastern Europe have the highest risk of stroke [6]. In Korea, stroke accounts for roughly 1 out of every 10 deaths, and the proportion of ischemic stroke has steadily increased [7]. To effectively care for patients with PV-associated CI, hematologists should communicate well with neurologists.

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REFERENCES

1. Kaifie A, Kirschner M, Wolf D, et al. Bleeding, thrombosis, and anticoagulation in myeloproliferative neoplasms (MPN): analysis from the German SAL-MPN-registry. *J Hematol Oncol* 2016; 9:18.
2. Martin K. Risk factors for and management of MPN-associated bleeding and thrombosis. *Curr Hematol Malig Rep* 2017;12: 389-96.
3. Enblom A, Lindskog E, Hasselbalch H, et al. High rate of abnormal blood values and vascular complications before diagnosis of myeloproliferative neoplasms. *Eur J Intern Med* 2015;26:344-7.
4. Ong E, Barraco F, Nighoghossian N, et al. Cerebrovascular events as presenting manifestations of myeloproliferative neoplasm. *Rev Neurol (Paris)* 2016;172:703-8.
5. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391-405.
6. GBD 2016 Lifetime Risk of Stroke Collaborators. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. *N Engl J Med* 2018;379:2429-37.
7. Hong KS, Bang OY, Kang DW, et al. Stroke statistics in Korea: part I. Epidemiology and risk factors: a report from the Korean Stroke Society and clinical research center for stroke. *J Stroke* 2013;15:2-20.

Beta-2 microglobulin as a prognostic factor of primary central nervous system lymphoma

TO THE EDITOR: Primary central nervous system lymphoma (PCNSL) is an extra-nodal non-Hodgkin lymphoma involving the brain, leptomeninges, eyes, or spinal cord and no primary malignancy outside of the central nervous system (CNS). PCNSL is a rare lymphoma and accounts for only 1% of all incident lymphomas [1, 2]. Prevalence of the disease is higher in the sixth to eighth decades of life. The median age at diagnosis of PCNSL is 65 years and the incidence is rising in the elderly population [3, 4].

Among several previously published prognostic models, the International Extranodal Lymphoma Study Group (IELSG) and the Memorial Sloan Kettering Cancer Center (MSKCC) models are the most widely used in current practice [5, 6]. Old age and poor performance status at initial diagnosis were strong poor prognostic factors commonly found in both studies. Meanwhile, serum beta-2 microglobulin (B2MG) is a well-established prognostic factor in multiple myeloma and follicular lymphoma [7, 8]. Thus,

the purpose of this study was to validate previously suggested prognostic factors and to evaluate prognostic value of serum B2MG level in PCNSL patients.

Methods

Patients

We retrospectively analyzed the PCNSL registry data for patients treated from March 1993 to May 2017 at the Asan Medical Center in Seoul, South Korea. Variables that were extracted from the medical records and analyzed included patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status, tumor characteristics, treatment profiles, serum lactate dehydrogenase (LDH) level (normal range <250 IU/L), serum B2MG level (normal range <2.5 µg/dL), cerebrospinal fluid (CSF) total protein level, number of CNS lesions, existence of deep CNS lesions (brain stem, thalamus, basal ganglia, and cerebellum), date of disease progression, and survival status.

Statistics

Overall survival (OS) was defined as the time from the beginning of first-line therapy to death from any cause. Univariate and multivariate analyses were performed to identify prognostic factors for OS using a Cox proportional hazards model. Survival curves were estimated by the Kaplan-Meier method and compared using log-rank tests. A two-sided *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp, Armonk, NY, USA).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required (IRB 2018-1275).

Results

Clinical characteristics

In total, 163 patients were identified and included in the analysis. The median follow-up duration was 3.5 years [95% confidence interval (CI), 2.4–4.6] and median OS was 4.0 years (95% CI, 2.1–5.9). Baseline patient characteristics are summarized in Table 1. The median age was 60 years (range, 19–83), 88 patients (54.0%) were 60 years of age or older and 89 patients (54.6%) were males. All patients received high-dose methotrexate-based chemotherapy as initial treatment. Human immunodeficiency virus (HIV) serology was checked in 67 patients at the time of diagnosis and all were negative.

Prognostic factors

Univariate analysis of prognostic factors revealed that poor performance status [Eastern Cooperative Oncology Group Performance scale (ECOG PS) ≥ 2] and elevated se-

rum B2MG (≥ 1.8 µg/mL) were significantly associated with shorter OS (Table 2). Old age (≥ 60 yr) showed borderline association in terms of poor OS [hazard ratio (HR) 1.55; 95% CI, 0.95–2.52; *P*=0.068]. Multivariate analysis results were consistent with HRs of 2.5 (95% CI, 1.06–3.03; *P*=0.001) for ECOG PS ≥ 2 and 1.79 (1.06–3.03; *P*=0.038) for elevated serum B2MG (≥ 1.8 µg/mL). The survival curves of the two groups according to serum B2MG level are shown on Fig. 1.

Discussion

In our analysis, ECOG PS higher than 1 and elevated

Table 1. Baseline clinical characteristics.

Variable	Patients (%) (N=163)
Age	
< 60	75 (46.0)
≥ 60	88 (54.0)
Sex	
Male	89 (54.6)
Female	74 (45.4)
Histology	
DLBCL	146 (89.6)
Not confirmed ^{a)}	17 (10.4)
ECOG performance status	
0–1	116 (71.2)
≥ 2	47 (28.8)
Serum LDH level	
> 250 IU/L	106 (65.0)
≤ 250 IU/L	57 (35.0)
N of CNS lesion	N=153
Single	77 (50.3)
Multiple	76 (49.7)
Existence of deep brain lesion	N=153
Yes	91 (59.5)
No	62 (40.5)
CSF protein level	N=140
≥ 68 mg/dL	48 (65.7)
< 68 mg/dL	92 (34.3)
Serum $\beta 2$ microglobulin level	
≥ 1.8 µg/dL	39 (23.9)
< 1.8 µg/dL	124 (76.1)
Best response after first line treatment	N=144
CR	69 (47.9)
PR	58 (40.3)
SD	1 (0.7)
PD	16 (11.1)
Patients who had ASCT	
Yes	58 (35.6)
No	105 (64.4)

^{a)}Not confirmed in histology means lymphoid malignancy without established exact diagnosis among NHL subtypes.

Abbreviations: ASCT, autologous stem cell treatment; CNS, central nervous system; CR, complete response; CSF, cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2. Univariate analysis and multivariate analysis of overall survival.

Variables	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age				
< 60	Reference			
≥ 60	1.55 (0.95–2.52)	0.068		
ECOG performance status				
0–1	Reference		Reference	
≥ 2	2.24 (1.38–3.63)	0.001	2.30 (1.06–3.03)	0.001
Serum LDH level				
≤ 250 IU/L	Reference			
> 250 IU/L	1.53 (0.94–2.48)	0.089		
Number of CNS lesions				
Multiple	Reference			
Single	0.88 (0.54–1.44)	0.616		
Presence of deep CNS lesion				
Yes	Reference			
No	1.15 (0.70–1.89)	0.583		
CSF protein level				
≥ 68 mg/dL	Reference			
< 68 mg/dL	1.18 (0.68–2.04)	0.552		
Serum β2 microglobulin				
< 1.8 μg/dL	Reference		Reference	
≥ 1.8 μg/dL	1.70 (1.01–2.88)	0.047	1.79 (1.06–3.03)	0.038

Abbreviations: CI, confidence interval; CNS, central nervous system; CSF, cerebrospinal fluid; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

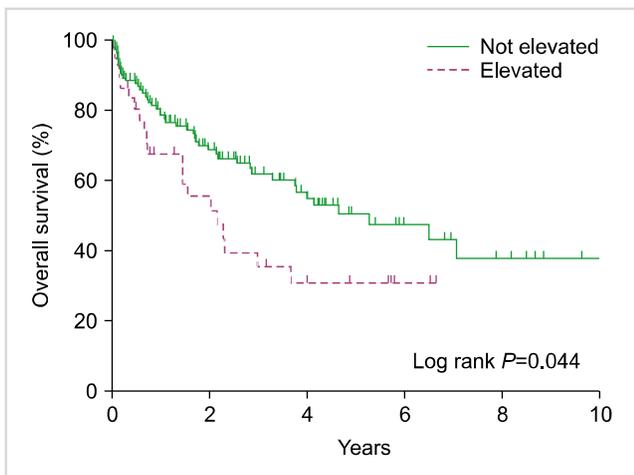


Fig. 1. Overall survival from the initiation of first-line treatment.

serum B2MG level were significantly predictive of poor prognosis according to univariate analysis. Most studies defined a cutoff level of serum B2MG level between 2.0 to 3.5 and our analysis showed 1.8 as the best cutoff level to establish a significant survival benefit [7-9]. Although the mechanism underlying the negative prognostic impact of elevated serum B2MG is unclear, a widely accepted hypothesis is that it is related to high tumor burden [9, 10]. Based on this hypothesis, we might explain the relatively low cutoff level of B2MG in PCNSL by reiterating that

even a small elevation of serum B2MG could reflect high tumor burden in the CNS. Our results are reliable considering the large number of enrolled patients and comparable survival outcomes of our cohort with other studies [6]. In the MSKCC study, 240 patients were enrolled, and the median OS and failure-free survival were 37 (95% CI, 31–42) months and 17 (95% CI, 12–21) months, respectively.

Our study has some limitations including the retrospective nature and also it is a single center study. Another limitation is that the cut-off value of B2MG level 1.8 μg/dL is arbitrary. However, the cutoff value in this study represents only a population from single center. Higher serum B2MG level could have some relationship with survival outcomes in PCNSL and further investigations via multi-center studies are needed. In conclusion, ECOG performance status and serum B2MG were associated with prognosis in PCNSL patients. Serum B2MG may have some association with prognosis of PCNSL.

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REFERENCES

- Haldorsen IS, Espeland A, Larsson EM. Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. *AJNR Am J Neuroradiol* 2011;32:984-92.
- van der Sanden GA, Schouten LJ, van Dijk JA, et al. Primary central nervous system lymphomas: incidence and survival in the Southern and Eastern Netherlands. *Cancer* 2002;94:1548-56.
- Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer* 2011;105:1414-8.
- O'Neill BP, Decker PA, Tieu C, Cerhan JR. The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin's lymphoma. *Am J Hematol* 2013;88:997-1000.
- Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. *J Clin Oncol* 2003;21:266-72.
- Abrey LE, Ben-Porat L, Panageas KS, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. *J Clin Oncol* 2006;24:5711-5.
- Munshi NC, Anderson KC, Bergsagel PL, et al. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood* 2011;117:4696-700.
- Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol* 2009;27:4555-62.
- Hagberg H, Killander A, Simonsson B. Serum beta 2-microglobulin in malignant lymphoma. *Cancer* 1983;51:2220-5.
- Shi C, Zhu Y, Su Y, Chung LW, Cheng T. Beta2-microglobulin: emerging as a promising cancer therapeutic target. *Drug Discov Today* 2009;14:25-30.

Long-term response in refractory AML following azacitidine-failed MDS by salvage decitabine-bridged allogeneic transplantation

TO THE EDITOR: Myelodysplastic syndromes (MDS) are a group of heterogeneous hematological malignancies which demand personalized and risk-adapted clinical management [1]. Current therapeutic approaches are rather limited for patients unsuitable for allogeneic stem cell transplantation (SCT), the only realistic and potentially curative treatment measure that exists [1]. With regard to patients with high risk MDS, the standard of care is currently represented by treatment with hypomethylating agents (HMAs), such as decitabine and azacitidine. The latter is used as initial therapy in most cases, and induces responses in 40–50% of treated patients [2, 3]. Obstacles to azacitidine administration as well as recommendations for the optimization of treatment with this agent have been reported [2, 4]. However, despite optimal management of azacitidine treatment, the duration of its clinical benefit, although variable, is usually transient and almost all patients ultimately experience loss of response to the drug, disease progression, and therefore very poor outcomes [1, 2, 5, 6]. After this loss of response or disease progression despite treatment, there are no standard care regimens available [5]. Rescue strategies including intensive chemotherapy (ICT) only provide minor benefits, whereas allogeneic SCT is feasible only in a minority of cases. With these results in mind, especially the catastrophic outcome of azacitidine-failed patients, typical concerns about decision making and clinical management in these settings can be summarized by an unusual case we observed which is reported herein. A 59-year-old woman was admitted for profound malaise due to pancytopenia on March 2015. The bone marrow (BM) and trephine biopsy revealed refractory anemia with an excess of blasts-2 (RAEB-2), remarkable multilineage dysplasia, and 18% of BM infiltrating blasts; the karyotype analysis and molecular study for typical abnormalities found in MDS were negative. She was diagnosed as having an Inter-2 MDS, according to the International Prognostic Scoring System [7]. On the basis of the patient's overall fitness level, and given the lack of a suitable familiar donor to proceed to immediate allogeneic SCT, we recommended therapy with azacitidine (75 mg/m², schedule 5+2+2). Therapy was started on April 2015 without significant adverse effects. Meanwhile, a matched unrelated donor (MUD) was fruitlessly sought. After six cycles (September 2015), a partial remission (according to Cheson's criteria) was achieved [8]. Because of this, the same treatment was continued for another three cycles until December 2015, when a progressive pancytopenia unveiled progression to secondary acute myelogenous leukemia (AML). At the time of evolution, standard