infection caused by nilotinib. However, nilotinib may also be a risk factor for TB by inhibiting T cell-mediated immune responses, similar to imatinib [8]. Steroids also inhibit immunity, so we cannot rule out the possibility that pulmonary Tb may be an effect of steroids. However, in our case, as the initial sputum AFB culture obtained before methylprednisolone therapy showed a positive result after 6 weeks of incubation, TB infection was the initial pathogenic event of the pulmonary symptoms and it is less likely that TB was caused by the steroid.

Drug resistance tests of the initial sputum indicated that the TB strain was sensitive to first-line drugs, but respiratory symptoms remained after sufficient treatment. This may have been due to drug-drug interactions (DDIs) between the antituberculosis medications and TKIs.

The patient was switched to second-line drugs due to drug resistance, with acceptable CML and TB treatment outcomes. DDIs between radotinib and antituberculosis medications have not been studied, so further pharmacological studies are required to understand DDIs and to determine the optimum doses of TKIs during antituberculosis therapy.

To the best of our knowledge, this is the first case report of TB developing during nilotinib treatment. In the case described, the clinical manifestations were those of atypical pneumonia, not those of typical pulmonary TB. Furthermore, because it takes at least 6 weeks for culture results for *Mycobacterium tuberculosis* to be reported, diagnosis and treatment of TB were delayed. As the clinical features of this case were not typical of TB infection, it was difficult to diagnose and properly manage the patient. Thus, when CML patients on nilotinib treatment suffer from atypical pneumonia which is unresponsive to conventional antibiotics, it is important to suspect TB infection and repeat sputum studies even if it is not diagnosed at once. In particular, in areas endemic for TB such as South Korea, the possibility of reactivation of TB in patients receiving treatment with nilotinib should be considered.

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What is the most appropriate regimen for untreated Waldenström macroglobulinemia? - An updated analysis of rituximab and half-dose CHOP therapy and cost effectiveness

TO THE EDITOR: Waldenström macroglobulinemia (WM) is a rare type of low-grade B-cell lymphoma in which overexpression of the IgM monoclonal protein occurs. In most cases of WM, an *L265P* mutation is present in *MYD88* [1], and approximately 30–50% of cases have a chromosomal 6q deletion [2]. Owing to its rarity, reports on therapies

from prospective randomized studies for WM are limited. We previously reported the impact of half-dose CHOP therapy [cyclophosphamide (CPA); hydroxy-doxorubicin (ADR); vincristine (VCR); and prednisone (PSL)] combined with the anti-CD20 antibody, rituximab (R) (R-half CHOP), for untreated patients with WM [3], because the standard-dose R-CHOP therapy [4, 5] caused severe myelosuppression and peripheral neuropathy (PN). Herein, we have presented the updated outcomes over the median follow-up period of 37.7 months.

Twenty-five untreated symptomatic patients with WM who received R-half CHOP as the primary therapy at our hospital between April 2011 and April 2017 were analyzed retrospectively. Approval from the Institutional Review Board of our hospital was obtained, and the study was performed according to the Declaration of Helsinki formulated in 1995. R-half CHOP consisted of 6 treatment cycles, with each cycle separated by 3 weeks; however, for 21 patients, vincristine was omitted. Two (8%) patients achieved complete response (CR), 1 (4%) patient achieved very good partial response (VGPR), 12 (48%) patients achieved partial response (PR), and 6 (25%) patients achieved minimal response (MR). The median follow-up of all 25 patients was 37.7 months (range, 12–83.2 mo). The median progression-free survival (PFS) was not reached, although the estimated 2-year and 3-year PFS was 72% and 64%, respectively (Fig. 1A). Nine patients developed refractory disease or progression. All patients received a bendamustine (Benda)-containing regimen as second-line therapy. Subsequently, 2 (22%) patients achieved VGPR and 6 (67%) achieved PR. The estimated 3-year second PFS was 89% (Fig. 1A). The estimated 3-year overall survival (OS) was 96% (Fig. 1B). A swimmer plot of patient responses is presented in Fig. 2. Grade 3/4 leukocytopenia, neutropenia, febrile neutropenia, and Grade 1 peripheral neuropathy (PN) occurred in 33%, 38%, 0%, and 21% of patients, respectively. During the follow-up, 3 patients died: 1 patient experienced traumatic subarachnoid hemorrhage with disease progression, 1 patient had Bing-Neel syndrome, and 1 patient who maintained CR committed suicide (Fig. 2). Furthermore, none of the patients had secondary malignancies. Thus, we confirmed that half-dose R-CHOP was effective and well-tolerated as the primary therapy for untreated WM. In addition, the use of a Benda-containing regimen as second-line therapy had a high response rate and favorable PFS. Therefore, half-dose R-CHOP as first-line therapy and Benda-containing regimen as second-line therapy would be an appropriate treatment strategy for newly diagnosed symptomatic WM.

Buske *et al.* [6] previously reported treatment and outcome patterns for 454 patients with WM outside of clinical trials between 2000 and 2014 in 10 European countries. One hundred and ninety-three (43%) patients received monotherapy including chlorambucil (Chl, 27%), and R (6%); 164 patients (36%) received R and alkylating agents (chemo-immunotherapy), such as R-CHOP (11%) [4, 5], and dexamethasone, R, and cyclophosphamide (DRC) therapy (6%) [7]. Olszewski *et al.* [8] reported patterns in treatment regimens associated with survival for patients of ≥65 years of age with WM for whom first-line rituximab-based therapy was initiated in 2008–2014 by using the Surveillance, Epidemiology, and End Results registry in the US. Of the 681 patients, 58% received R alone, 22% received chemo-immunotherapy, 11% received a bortezomib (Bor)-containing regimen, and 9% received a Benda-containing regimen. They also found no significant difference in OS between immune-chemotherapy combinations with classical agents and those with Bor-containing or

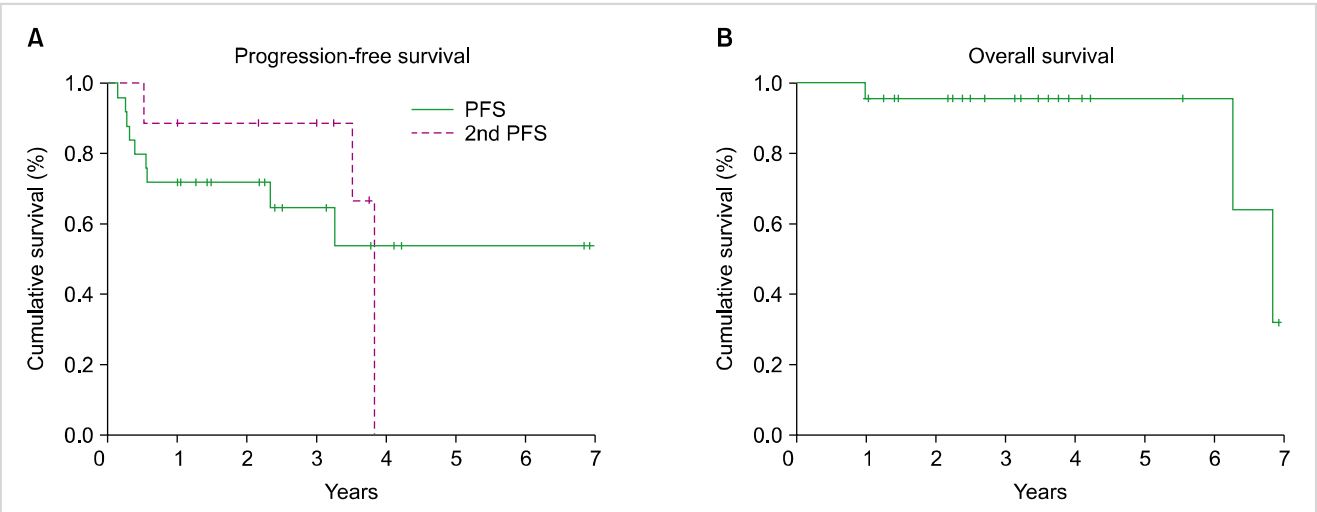

Fig. 1. Survival curve. **(A)** Progression-free survival (PFS). The median PFS of half-dose R-CHOP therapy was not reached, and the estimated 2-year PFS was 72% and 3-year PFS was 64%. The estimated 3-year second PFS by a bendamustine-containing regimen was 89%. **(B)** Overall survival (OS). The estimated 3-year OS was 96%.

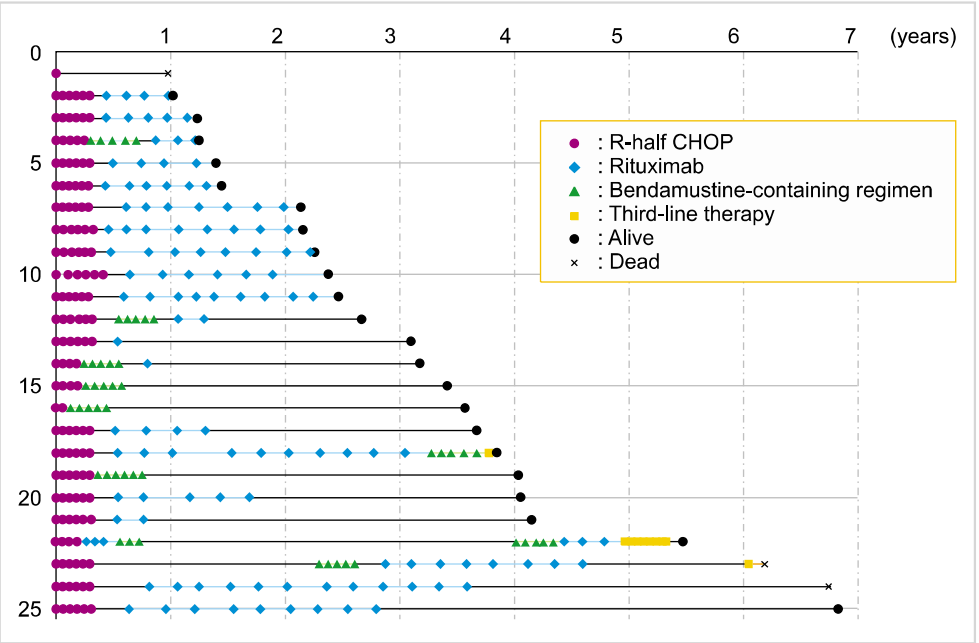

Fig. 2. Swimmer plot for 25 patients who received half-dose R-CHOP therapy. Nine patients developed refractory disease or progression and 3 patients received third-line therapy.

Table 1. Summary of responses to each regimen, survival, and drug prices.

Regimen	First author	Ref No.	N	Duration of treatment	ORR	Time to response	Survival	Drug prices (JPY)
DRC	Dimopoulus	7	72	18 wk	83%	4.1 mo	35 mo (mPFS)	1,345,014/total
R-CHOP	Buske	4	23	18 wk	91%	NA	63 mo (mTTF)	1,479,936/total
Half-dose R-CHOP	Present study		25	18 wk	85%	5.7 wk	64% (3-yr PFS)	1,425,612/total
R-bendamustine	Rummel	5	22	24 wk	95%	NA	69.5 mo (mPFS)	3,526,806/total
BDR	Treon	11	23	60 wk	96%	1.4 mo	NR (mTTP≥30 mo)	6,182,104/total
Ibrutinib[a)]	Treon	12	63[b)]	Until PD	90.5%	4 wk	69.1% (2-yr PFS)	10,895,797/yr

[a)]Ibrutinib is not approved in Japan for WM. [b)]Data relapsed/refractory WM.
Abbreviations: R, rituximab; DRC, dexamethasone, R, cyclophosphamide; R-CHOP, R, cyclophosphamide, hydroxyl-doxorubicin, vincristine, prednisone; BDR, bortezomib, dexamethasone, R; ORR, overall response rate; JPY, japanese yen; PFS, progression-free survival; TTF, time to treatment failure; TTP, time to progression; PD, progressive disease; NA, not applicable; NR, not reached.

Benda-containing regimens, although the proportion of Benda- or Bor-containing regimens increased significantly between 2008 and 2014. In studies from Asia, Lee *et al.* [9] reported the prevalence of Chl alone (35.2%) followed by an alkylating regimen (±R, 28.2%) in a Korean study. This was similar in Japan, with Saito *et al.* reporting the prevalence of oral alkylating agent therapy alone (46.5%) and CHOP-like regimens (25.4%) [10]. Therefore, the regimens of R alone, oral alkylating agents alone, and R+alkylating agent regimens, including R-CHOP therapy, are popular, according to clinical treatment data.

In a consideration of the costs of WM therapy, Olszewski *et al.* [8] reported no apparent survival benefit and higher costs of treatment for Bor- or Benda-containing regimens. Thus, their value compared with classical regimens should be reconsidered in US practice. We also calculated the drug prices of each regimen in Japanese yen, as shown in Table 1. The prices were calculated for a patient with a body-surface area (BSA) of 1.74 m^2, which was the average BSA of Japanese men between 65 and 69 years of age in 2017. The costs of Benda-containing regimens and Bor-containing regimens [11] were more than 2 and 4 times higher than those for R-alkylating regimens, respectively.

Furthermore, novel agents, such as ibrutinib (Ibr), have been developed for WM. Ibr is an orally administered inhibitor of Bruton's tyrosine kinase (BTK). In 2015, it was approved by the US Food and Drug Administration and the European Medicine Agency for adults with relapsed/refractory WM or for previously untreated patients with WM for whom treatment with chemo-immunotherapy is not suitable [12, 13]. Ibr monotherapy was highly active, associated with sustainable responses, and safe [12], and the use of Ibr with R resulted in a significantly higher PFS than the use of R alone [13]. However, as the cost of Ibr treatment is very high, Olszewski *et al.* [14] examined the cost-effectiveness of Ibr use compared with che-

mo-immunotherapy. Italian medical and economical experts analyzed the cost-effectiveness of single-agent Ibr compared with the Italian current therapeutic pathways (CTP) for relapse/refractory WM by using an incremental cost-effectiveness ratio [15]. They concluded that Ibr increased the Life Years Gained and costs were comparable with CTP. These reports have confirmed the need for additional analyses of the cost-effectiveness of each drug and regimen, including Ibr.

In conclusion, numerous drugs are available currently; however, in addition to the drug approval status, the age of patients to be treated, presence of severe symptoms such as hyperviscosity syndrome, treatment period, response rate, long-term survival rate, secondary malignancies, costs, and any other relevant factors, should be comprehensively examined to allow making an informed decision on the treatment regimen.

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