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REPLY FROM THE AUTHORS

We have reviewed the commentary by Sookaromdee and Wiwanitkit and our reply is as follows.

We observed a patient with long-term multiple myeloma (MM) and an infrequent infection with *Cystoisospora belli* [1]. An intestinal-type chronic diarrhea was the only symptom contributing to the diagnosis. We wished to emphasize awareness of *C. belli* infection in MM patients. Sookaromdee and Wiwanitkit are of the same opinion as they mentioned the importance of *C. belli* infection in MM patients and emphasized that recommendations should be developed based on regional characteristics, especially in relation to poor hygiene conditions. They also cited an original study reported from Brazil to demonstrate that the infection could be observed in this patient population [2]. The mentioned study included 47 hematological malignancy patients and evaluated the infectious complications in patients who underwent autologous stem cell transplantation. The number of MM patients was 29. The study did not specify infectious agents according to primary diagnosis. The only result given in that study that might be pertinent for *C. belli* infection was that the authors observed 7 coccidia cases. Coccidia subgroups were not defined. For that reason, we did not cite that study in our original manuscript. Indeed, our aim was similar to that of Sookaromdee and Wiwanitkit; when treating MM patients from variable hygienic backgrounds with the complication of diarrhea, *C. belli* should be considered. Thus, the letter above supports our original argument.

Tarık Onur Tiryaki, Kadir Uluç Anıl, Melek Büyük, Ahmet Yasir Yıldırım, Alp Atasoy, Aslı Çiftçibaşı Örmeci, Sevgi Kalayoğlu Beşışık

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Lenalidomide Combined with Interferon α-1b and Interleukin-2 in the Treatment of 21 Cases of Acute Myeloid Leukemia

Yirmi Bir Akut Myeloid Lösemi Olgusunda İnterferon α-1b ve Interlökin-2 ile Birlikte Lenalidomid Tedavisi

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To the Editor,

The prognosis of patients with refractory/relapsed acute myeloid leukemia (R/R AML) is extremely poor and the long-term survival rate is less than 10%. Minimal residual disease (MRD) is an important independent prognostic indicator of AML, indicating a higher risk of recurrence; thus, it is vital for the prognosis of patients to eliminate MRD [1,2]. Our center previously used thalidomide combined with interferon α-1b (IFN α-1b) and interleukin-2 (IL-2) in the treatment of R/R AML and the total effective rate was 50% [3,4]. We further optimized the treatment plan, adjusted thalidomide to lenalidomide, and applied it for 21 patients with R/R AML or MRD.

All patients were treated with lenalidomide combined with the IFN α-1b and IL-2 regimen. The specific treatment plan was as follows: oral administration of lenalidomide capsule,

10-25 mg, every night; IFN-α1b, 60 μg; and IL-2, 1,000,000 U subcutaneous injection, once every other day. Each treatment cycle lasted 4 weeks. This retrospective analysis was approved by the Institutional Review Board of Henan Cancer Hospital.

Among 17 patients with R/R AML, 7 patients had complete remission (CR), 2 had CR with incomplete recovery of blood cells (CRi), and 8 had no remission. One patient in the low-risk group achieved CR, while the remission rate in the intermediate-risk group and high-risk group was 57.1% (4/8) and 50% (4/8), respectively. Of 3 patients with *TET2* mutations, 2 patients achieved remission; 6 patients with *FLT3-ITD/TKD* mutations were given sorafenib at the same time and 3 patients achieved remission. Particularly, among the 4 MRD-positive patients with remission of AML, the MRD of 3 patients was lower than before and the MRD of 1 patient was higher than before. These patients' clinical data are presented in Table 1. The total effective rate (CR+CRi+MRD decreased) of 21 patients was 57.1%. No treatment-related deaths occurred. The median overall survival time of the 21 patients was 26 months (9-89 months), and the 3-year survival rate reached 42.9%. Among patients with effective application of this regimen, the duration of relief ranged from 2 to 28+ months.

IFN can directly kill AML by inhibiting growth-promoting cytokines, inducing apoptosis, and inhibiting cell proliferation. Meanwhile, it is possible to indirectly target AML cells through the immunostimulatory effects of interferon on dendritic cells, T-cells, and natural killer (NK) cells [5,6]. IL-2 increases the proliferation and activity of cytotoxic T-cells, NK-cells, and killer cells activated by lymphokines. It can also promote the secretion of antibodies and interferon to play an anti-tumor role [7]. Lenalidomide promotes tumor cell apoptosis by inhibiting the secretion of tumor necrosis factor α, IL-1, and IL-12. It also produces an anti-tumor effect by inhibiting the secretion of overexpressed vascular endothelial growth factor [8,9,10].

The combination of lenalidomide, IFN α-1b, and IL-2 showed improvements in efficacy and safety profiles as compared to monotherapy among patients with R/R AML, and especially in the elimination of MRD, and it may become a promising treatment regimen.

Keywords: Acute myeloid leukemia, Refractory/relapsed, Minimal residual disease, Lenalidomide, Interferon α-1b, Interleukin-2

Anahtar Sözcükler: Akut myeloid lösemi, Dirençli/nüks, Minimal kalıntı hastalık, Lenalidomid, İnterferon α-1b, İnterlökin-2

Table 1. Clinical data of 21 patients with refractory/relapsed or minimal residual disease-positive acute myeloid leukemia treated with lenalidomide combined with interferon α-1b and interleukin-2.

No.	Sex	Age (years)	Karyotype at first diagnosis	Gene mutation	FAB typing	NCCN risk category	Status	Marrow blasts (%) before the application of the regimen	Bone marrow cellularity	Remission status	Duration of remission (months)	OS (months)
1	F	53	Normal	*TET2*	M2a	Intermediate	Refractory	14%	Hypocellular	CR	5	16
2	M	63	Complex karyotype	*TET2*	M2a	High	Refractory	39%	Normocellular	NR	-	9
3	M	59	Normal	(-)	M5b	Intermediate	Refractory	68%	Hypercellular	NR	-	11
4	F	36	Normal	*U2AF1*	M0	Intermediate	First relapse	53%	Normocellular	NR	-	20
5	F	57	Normal	*FLT3-ITD*	M1	High	Second relapse	10%	Normocellular	NR	-	15
6	M	60	Normal	*FLT3-ITD, IDH1, NPM1*	M1	Intermediate	First relapse	1.6%	Normocellular	CR	4	26
7	F	60	Normal	(-)	M2a	Intermediate	Second relapse	12.5%	Hypocellular	CRi	20	71
8	F	65	Normal	*DNMT3A*	M2a	High	First relapse	5%	Normocellular	CR	8	17
9	M	61	Normal	*ASXL1, PHF6*	M2a	High	Second relapse	12.5	Hypocellular	CR	7	44
10	F	66	Normal	(-)	M2a	Low	Second relapse	14.8%,	Normocellular	NR	-	89
11	F	59	46,XX,t(8,21)(q22,q22)	*C-KIT*	M2b	Intermediate	Second relapse	7.9%	Normocellular	CRi	11	54

Table 1. Continued.

No.	Sex	Age (years)	Karyotype at first diagnosis	Gene mutation	FAB typing	NCCN risk category	Status	Marrow blasts (%) before the application of the regimen	Bone marrow cellularity	Remission status	Duration of remission (months)	OS (months)
12	M	68	46,XY,t(8;21)(q22;q22)	*FLT3-ITD*	M2b	High	Second relapse	9.8%	Normocellular	CR	14	53
13	M	59	Normal	*FLT3-ITD*	M4	High	First relapse	4.8%	Hypocellular	NR	-	22
14	M	67	47,XY,+8[10]	(-)	M4	Intermediate	First relapse	12.4%	Normocellular	NR	-	28
15	M	55	Normal	*FLT3-TKD, DNMT3A, NPM1*	M5	High	First relapse	27.2%	Normocellular	NR	-	20
16	F	58	Normal	*TET2*	M5b	Intermediate	First relapse	48%	Hyperactive	CR	2	18
17	F	43	Normal	*FLT3-ITD, NPM1*	M7	High	First relapse	12.2%	Normocellular	CR	9	20
18	M	28	46,XY,t(8;21)(q22;q22)[10]	(-)	M2a	Low	CR with MRD+	0%, AML-ETO/ABL 0.010%	Hypocellular	CR	22	37
19	M	38	46,XX,t(8,21)(q22,q22)[20]	(-)	M2b	Low	CR with MRD+	0.2%, AML-ETO/ABL 0.082%	Normocellular	CR	23	51
20	M	47	46,XY,inv(16)(p13q22)[17]	*IKZF1, ERG, MLL-PTD*	M4	Low	CR with MRD+	0%, CBFB-MYH11A/ABL 0.016%	Normocellular	CR	-	41
21	M	58	46,XY,add(12)(q24)(8)/47,idm,+8(2)	*IDH2, TET2*	M5b	High	CR with MRD+	0.8%, WT1/ABL 0.40%	Hypocellular	CR	28	52

FAB: French-American-British; NCCN: National Comprehensive Cancer Network; OS: overall survival; CR: complete remission; MRD: minimal residual disease; CRi: CR with incomplete recovery of blood cells; NR: no remission.

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