



Letter to the Editor

Is there any difference between busulfan-cyclophosphamide and cyclophosphamide-busulfan in patients underwent allogeneic transplantation?

Dear Editor,

Busulfan (Bu) and cyclophosphamide (Cy) are frequently used chemotherapeutic agents in conditioning regimens given before allogeneic and autologous stem cell transplantation. The Bu-Cy regimen, which is the combination of these two agents, is the most studied conditioning regimen that leads to deep remission especially in young acute myeloid leukemia (AML) patients who undergoing allogeneic transplantation. Bu-Cy is a myeloablative conditioning regimen and is recommended for AML patients under 45 years of age.¹

In a study examining the pharmacokinetic interaction between Bu and Cy, it was found that administration of Cy immediately after Bu treatment increased exposure to Cy and its active metabolite. A negative association was found between the time interval between Cy and Bu administration and the exposure to Cy and its active metabolite.²

The scheme of administration of the Bu-Cy regimen is as follows: 3.2 mg/kg/day Bu is administered for a total of 16 doses between days -7 and -4, followed by 60 mg/kg/day Cy on days -3 and -2. A reduction in transplant-related mortality and sinusoidal obstruction syndrome (SOS) incidence was demonstrated by administration of Cy on days -8 and -7 followed by Bu for days -6 to -2 (Cy-Bu regimen) in retrospective studies.^{3,4}

Because the results from retrospective studies need to be confirmed with a prospective randomized trial, Seydoux et al. designed a multicenter randomized controlled trial. In this study, clinical outcomes of 33 patients given Bu-Cy and 37 patients given Cy-Bu prior to allogeneic transplantation and toxicities of the regimens were compared.⁵ In this study, a 24-h interval was left between Bu and Cy administration, as it was determined in previous studies that shortening the time interval between Bu and Cy can reduce toxicity.² While the baseline characteristics of the groups were similar, liver toxicity, SOS incidence, and 4-year non-relapse mortality in patients receiving the Cy-Bu regimen were found to be lower than those who received Bu-Cy (all $p \leq 0.05$). However, the rates of acute and chronic graft versus host disease and neutrophil and platelet

engraftment times of the groups were similar. Although there was 24 h between Bu and Cy administrations in both groups, less toxicity was found in patients who received the Cy-Bu regimen, indicating that the displacement of the administration order of the drugs is an important factor in reducing toxicity.

Based on the recently published randomized controlled trial and other retrospective studies, we recommend the use of the Cy-Bu regimen instead of Bu-Cy, a conditioning regimen very commonly used in young fit patients in transplant centers. We think that clinicians will observe significant improvements in patient outcomes just by changing the order of administration of drugs.

Funding

None.

Conflicts of interest

None.

Acknowledgements

None.

REFERENCES

1. Jethava YS, Sica S, Savani B, Socola F, Jagasia M, Mohty M, et al. Conditioning regimens for allogeneic hematopoietic stem cell transplants in acute myeloid leukemia. *Bone Marrow Transplant.* 2017;52(11):1504–11.
2. Hassan M, Ljungman P, Ringdén O, Hassan Z, Oberg G, Nilsson C, et al. The effect of busulphan on the pharmacokinetics of cyclophosphamide and its 4-hydroxy metabolite: time interval

- influence on therapeutic efficacy and therapy-related toxicity. *Bone Marrow Transplant.* 2000;25(9):915–24.
3. Cantoni N, Gerull S, Heim D, Halter J, Bucher C, Buser A, et al. Order of application and liver toxicity in patients given BU and CY containing conditioning regimens for allogeneic hematopoietic SCT. *Bone Marrow Transplant.* 2011;46(3):344–9.
 4. Kumar R, Kapoor R, Das SR, Yanamandra U, Pramanik S, Sharma S, et al. Cyclophosphamide followed by intravenous busulfan (Cy-Bu) as myeloablative conditioning: impact on venoocclusive disease and transplant outcomes, real world experience. *Blood.* 2017;130(Supplement 1):3226.
 5. Seydoux C, Medinger M, Gerull S, Halter J, Heim D, Chalandon Y, et al. Busulfan-cyclophosphamide versus cyclophosphamide-busulfan as conditioning regimen before allogeneic hematopoietic cell transplantation: a prospective randomized trial. *Ann Hematol.* 2021;100(1):209–16.

Ömer Faruk Bahçecioğlu ^{*,a}, Selim Gök ^a, Mefkür Durmuş ^a, Ahmet Sarıcı ^b

^a İnönü University Faculty of Pharmacy, Department of Clinical Pharmacy, Malatya, Turkey

^b İnönü University Faculty of Medicine, Department of Hematology, Malatya, Turkey

*Corresponding author at: İnönü University Faculty of Pharmacy, Department of Clinical Pharmacy, 44280 Battalgazi/Malatya, Turkey.

E-mail address: omerfb92@hotmail.com (Ö.F. Bahçecioğlu).

Received 29 March 2021

Accepted 13 June 2021

Available online 31 July 2021

<https://doi.org/10.1016/j.htct.2021.06.005>
2531-1379/

© 2021 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).