EFFICACY OF HETROMBOPAG IN TREATING CHEMOTHERAPY-RELATED THROMBOCYTOPENIA AND ITS IMPACT ON THE IMMUNE MICROENVIRONMENT IN PATIENTS WITH DIGESTIVE SYSTEM MALIGNANCIES: A CLINICAL STUDY

Affiliation
Tongji Hospital, Huazhong University of Science and Technology, Wuhan,Hubei,China.

Corresponding author: Prof. Hong Qiu,
Department of Oncology, Tongji Hospital, Huazhong University of Science and Technologyt, 1095 Jiefang Avenue, Wuhan , Hubei, China, 430030, China.
E-mail: _. ORCID:

Abstract

Background: Patients with malignant digestive system tumors using oxaliplatin based chemotherapy often have thrombocytopenia, which is difficult to correct.

Methods: In patients with digestive system malignancies experiencing oxaliplatin-associated Grade II-III thrombocytopenia, Hetrombopag was administered prospectively until platelet counts reached ≥100×10^9/L, increased by ≥50×10^9/L from baseline, or for a maximum duration of 14 days. Retrospective analysis was conducted on clinical data from historical controls using concomitant rhTPO (recombinant human thrombopoietin) combined with Hetrombopag for Grade 2-3 oxaliplatin-induced thrombocytopenia. Propensity score matching was employed to analyze treatment response rates, median time to platelet recovery, and adverse reactions. Peripheral blood mononuclear cell (PBMC) samples collected before and after Hetrombopag treatment in a subset of patients underwent mass cytometry analysis to investigate alterations in the peripheral blood immune microenvironment.

Results: After propensity score matching, the response rate was 84.6% in the monotherapy group (Hetrombopag alone) versus 94.9% in the combination therapy group (Hetrombopag + rhTPO) (P = 0.263). The median time to platelet recovery was 9 days (95% CI 5.9–12.1) in the Hetrombopag group compared to 7 days (95% CI 4.6–9.4) in the combination group (P = 0.043). Both groups demonstrated comparable adverse event profiles. Post-treatment alterations in the peripheral blood immune microenvironment included M2 macrophage polarization, decreased CD38+ B-cell levels, and reduced proportions of regulatory T cells (Tregs).

Conclusion: In patients with digestive system malignancies with oxaliplatin-associated thrombocytopenia, both Hetrombopag monotherapy and Hetrombopag combined with rhTPO demonstrated safe and effective amelioration of thrombocytopenia. Additionally, Hetrombopag treatment exhibited modulatory effects on the peripheral blood immune microenvironment in these patients.

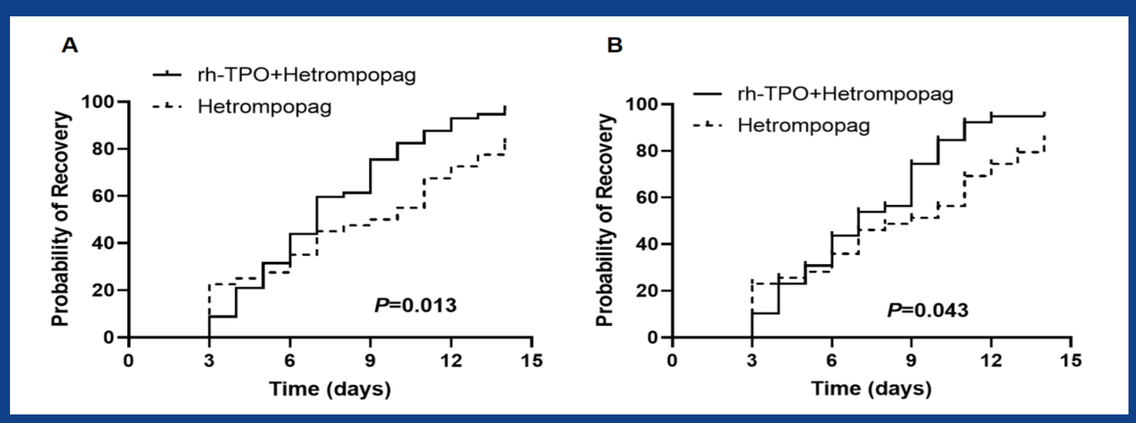

Figure 1 Platelet recovery curves before (A) and after (B) PSM

Therapeutic index	pre-PSM			post-PSM		
	Hetrombopag（n=40）	Hetrombopag+rhTPO（n=57）	P	Hetrombopag（n=39）	Hetrombopag+rhTPO（n=39）	P
Days of platelet recovery to ≥75×109/L			0.013			0.043
Median (95% CI)	9.00（4.4-13.6）	7.0 (6.2-7.8)		9.00（5.9-12.1）	7.0 (4.6-9.4)	
Platelet increases from baseline were 50×109/L or 75×109/L			0.047			0.263
N（Effective rate，95% CI）	33（82.5，70.2- 94.8）	55（96.5, 92.4-102.6）		33（84.6, 72.8- 96.5）	37（94.9, 87.6-102.1）	
The lowest platelet value after treatment			0.218			1.000
Median	63.0	62.0		65.0	61.0	
Minimum, Maximum	17.0, 110.0	30, 114		17,110	34,114	
Maximum platelet value after treatment			0.002			0.359
Median	106.5	102		106.0	100.0	
Minimum, Maximum	35.0, 186.0	74.0, 203.0		35.0, 186.0	74.0, 490.0	
The maximum platelet value changed from baseline after treatment			0.031			0.169
Median	49.0	40.0		49.0	38.0	
Minimum, Maximum	-13.0, 15.0	6.0, 143.0		-13.0, 150.0	12.0, 429.0	
Platelet value on day 21			0.620			0.908
Median	98.0	95.5		97.0	97.5	
Minimum, Maximum	10.0，269.0	30.0，315.0		30, 315	10. 296	
Whether to affect the next cycle of treatment			0.469			0.187
YES	14（35.0%）	11（37.5%）		14(35.9%)	9(23.1%)	

Table 2 Primary and secondary outcomes before and after PSM

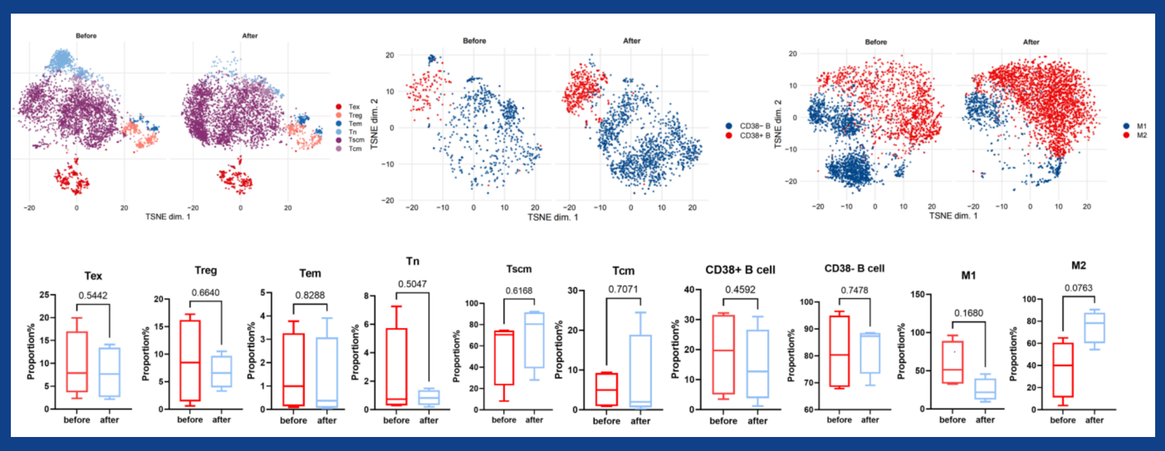

Figure 2 Changes of CD4+T cells, B cells and macrophage subsets before and after treatment with hexapopal

Yuhong Dai1, Ping Qiu2, Lei Wang3, Pengbo Hu1, Qiuyun Guo1, Li Sun1, Xianglin Yuan1, Weiheng Zhao1, Hong Qiu1
1.Department of Oncology, Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science & Technology, Wuhan, Hubei, People's Republic of China.
2.Department of Oncology, Jingzhou Central Hospital, Jingzhou, Hubei, People's Republic of China.
3.Department of Oncology, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang, Hubei, People's Republic of China.
一作：Yuhong Dai1, Ping Qiu2, Lei Wang3
通讯：Weiheng Zhao1, Hong Qiu1
Hong Qiu, qiuhong@hust.edu.cn
Yuhong Dai, eier_dai@163.com
Qiuyun Guo, happyyun.1985@163.com
Sun Li, litchisun@163.com
Wang Lei, 18271281231@163.com
Xianglin Yuan, yuanxianglin@hust.edu.cn
Pengbo Hu, d202482475@hust.edu.cn
Weiheng Zhao, zhaoweiheng319420@163.com

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