·临床研究·

重组人血小板生成素治疗老年滑膜肉瘤患者化疗后血小板下降的疗效观察

汪东昱[1],贾宝森[2],毕文志[1]*
(解放军总医院:[1]骨科,[2]麻醉手术中心,北京 100853)

【摘 要】 **目的** 探究重组人血小板生成素治疗老年滑膜肉瘤患者化疗中发生的血小板下降的疗效,为临床用药提供指导。**方法** 选择解放军总医院骨科2011年4月至2015年6月收治的滑膜肉瘤老年患者60例,全部采用MAID化疗方案,随机分为两组,A、B两组患者分别在第二化疗周期和第一化疗周期化疗给药结束后24 h内应用重组人血小板生成素注射液(15 000 U,1次/d,持续7 d或外周静脉血小板计数≥100×10^9/L时停药)。两组患者两次化疗间隔为14~21 d,血象复查全部指标在正常范围内后开始第二周期化疗,当患者血小板计数≤25×10^9/L时输注机采血小板。两组患者化疗期间其他辅助用药全部相同。观察患者化疗后外周血血小板最低值、恢复到的最高值、恢复至100×10^9/L所用时间、血小板≤50×10^9/L的持续时间,输注机采血小板的人次及数量。**结果** (1)两组患者在一般情况方面差异无统计学意义($P>0.05$)。(2)在相同化疗周期内用药组与对照组比较,血小板最低值有明显提升($P<0.05$),血小板最高值无明显差异($P>0.05$),而恢复时间、血小板≤50×10^9/L的持续时间、输注血小板人次及数量明显下降,差异有统计学意义($P<0.05$)。(3)两组患者自身的用药周期与对照周期相比,血小板最低值有明显提升($P<0.05$),血小板最高值无明显差异($P>0.05$),而恢复时间、血小板≤50×10^9/L的持续时间、输注血小板人次及数量明显下降,差异有统计学意义($P<0.05$)。**结论** 重组人血小板生成素可有效提升老年滑膜肉瘤患者化疗后的外周血血小板数量,使患者能够接受最优剂量化疗,保证化疗效果,且其不良反应较少,安全性好,适宜在临床推广应用。

【关键词】 老年人;重组人血小板生成素;滑膜肉瘤;疗效
【中图分类号】 R592;R738.5 【文献标识码】 A 【DOI】 10.11915/j.issn.1671-5403.2016.05.085

Efficacy of recombinant human thrombopoietin in treatment of chemotherapy induced thrombocytopenia in the elderly with synovial sarcoma

WANG Dong-Yu[1], JIA Bao-Sen[2], BI Wen-Zhi[1]*
([1]Department of Orthopedics, [2]Center for Anesthesia and Operation, Chinese PLA General Hospital, Beijing 100853, China)

【**Abstract**】 **Objective** To determine the efficacy of recombinant human thrombopoietin in the treatment of thrombocytopenia in the elderly patients with synovial sarcoma after chemotherapy. **Methods** Sixty elder patients with pathologically verified synovial sarcoma admitted in our Orthopedic Department during April 2011 and June 2015 were enrolled in this study. They were randomized into Group A and Group B, and were all treated with MAID chemotherapy (mesna, doxorubicin, ifosfamide, and dacarbazine). The patients from Group A did not receive recombinant human thrombopoietin in the first cycle of chemotherapy, but received within 24 h after the end of second cycle, at the dose of 15 000 U/d for 7 consecutive days or till the peripheral platelet count ≥100×10^9/L. For the patients of Group B, the protocol of thrombopoietin treatment was opposite to that of Group A. The interval of 2 cycles of chemotherapy was 14–21 d. The second cycle of thermotherapy started only when all the blood indicators were in the normal ranges. The patients were given platelet transfusion when the blood platelet count ≤25×10^9/L. Other adjuvant treatments were consistent between the groups. Minimal platelet count, recovery maximal platelet count, recovery time, duration to platelet count ≤50×10^9/L, platelet transfusion times and units were recorded to evaluate the efficacy. **Results** (1) No significant differences were observed in baseline data between the 2 groups ($P>0.05$). (2) Minimal platelet counts were elevated ($P<0.05$), but maximal platelet counts remained unchanged in

收稿日期:2016-01-27;**修回日期**:2016-03-13
基金项目:国家自然科学基金(81472513)
贾宝森,为共同第一作者
通信作者:毕文志,E-mail:biwenzhipaper@163.com

the thrombopoietin treatment group during both chemotherapy cycles ($P>0.05$). Recovery time, duration to platelet count $\leqslant 50\times10^9$/L, and platelet transfusion times and units were decreased significantly in the treatment group than in the control group ($P<0.05$). (3) Minimal platelet counts were increased ($P<0.05$) and maximal platelet counts remained the same in the treatment cycle of both groups ($P>0.05$). Recovery time, duration to platelet counts $\leqslant 50\times10^9$/L, and platelet transfusion times and units were reduced remarkably in the treatment cycle than the un-treatment cycle in both groups ($P<0.05$). **Conclusion** Recombinant human thrombopoietin effectively promotes the platelet counts in the elder synovial sarcoma patients after chemotherapy, and improves the patients to accept optimal doses of chemotherapeutic drugs for better overall efficacy. It is safe and of few side effects, and thus worth of extensive clinical application.

【Key words】 aged; recombinant human thrombopoietin; synovial sarcoma; efficacy

This work was supported by the National Natural Science Foundation of China (81472513).

WANG Dong-Yu and JIA Bao-Sen are co-first authors who contributed equally to this work.

Corresponding author: BI Wen-Zhi, E-mail: biwenzhipaper@163.com

滑膜肉瘤(synovial sarcoma)是一种软组织恶性肿瘤,由于其恶性程度较高,易转移,预后不良等,给患者带来极大痛苦。据文献报道,滑膜肉瘤占全部软组织肿瘤发病的5%~10%[1]。目前应用新辅助化疗配合手术切除治疗滑膜肉瘤获得良好效果,5年无转移生存率可达60%~70%[2-4]。但化疗同时也存在着一定风险,老年患者尤为突出,轻者可有头痛、呕吐等症状,重者则可因骨髓抑制所致的血小板下降继发大出血,产生致命风险。为防治血小板降低,患者往往无法接受最佳治疗剂量,影响化疗效果。重组人血小板生成素通过刺激巨核细胞生长及分化,促进前体细胞的增殖和多倍体巨核细胞的发育成熟,并能特异性升高外周血血小板数目,具有与内源性血小板生成素(TPO)相似的升高血小板的作用,能够有效对抗化疗所产生的血小板下降,减少患者出血风险并能使患者接受最佳化疗剂量[5-7]。本研究采用随机分组、自身前后对照的方式,对重组人血小板生成素治疗老年滑膜肉瘤患者化疗后血小板下降的效果进行观察,总结分析其临床疗效并评估其可行性。

1 对象与方法

1.1 研究对象

选择2011年4月至2015年6月解放军总医院骨科收治的滑膜肉瘤老年患者60例(年龄>60周岁)。男性患者35例,女性患者25例,年龄66~78岁,身高156~180 cm,体质量52~68 kg,体表面积1.60~1.88 m^2。入组条件:预计生存期>3个月;卡氏行为状态(Karnofsky performance status, KPS)评分>70分;年龄>60周岁;经我院病理科确诊;ⅡA~ⅡB期的原发性滑膜肉瘤;首次进行化疗;化疗前未行放疗且化疗中不同步放疗;化疗前未有发热等全身炎症表现且外周静脉血像正常;高血压及糖尿病等基础疾病控制良好;所有患者均签署化疗知情同意书及临床试验知情同意书。

1.2 研究方法

1.2.1 化疗方案及治疗药物 所有患者皆采用MAID方案进行化疗,即达卡巴嗪,异环磷酰胺,美司钠及多柔比星4种药物联合治疗,用药时间共5 d。重组人血小板生成素注射液(特比澳,沈阳三生制药有限公司)。

1.2.2 分组及给药方法 60例患者随机分为A和B两组,两组化疗方案相同,剂量根据患者体表面积决定。A、B两组患者分别在第二周期和第一周期全部化疗给药结束后24 h内应用重组人血小板生成素注射液(15 000 U,1次/d,持续7 d或外周静脉血小板计数$\geqslant 100\times10^9$/L时停药)。两次化疗间隔为14~21 d,血像复查全部指标在正常范围内后开始第二周期化疗,当患者血小板计数$\leqslant 25\times10^9$/L时输注机采血小板。两组患者化疗期间其他辅助用药全部相同。

1.2.3 观测指标 从化疗第1天起隔天监测患者外周静脉血血小板计数,持续14 d,当患者血小板计数$\leqslant 25\times10^9$/L时每日监测血常规。记录患者血小板最低值和之后所恢复到的最高值,及血小板由最低值恢复至100×10^9/L的时间(恢复时间)、血小板$\leqslant 50\times10^9$/L的持续时间、输注机采血小板人次及数量。

1.3 统计学处理

采用Graph Pad Prism 5统计软件进行数据处理。计量资料表示为均数±标准差($\bar{x}\pm s$),检验方式选择独立样本t检验(Student's t test)、配对t检验(paired t test)及Welch近似t检验(Welch's t test);计数资料以百分率表示,组间比较采用χ^2检验。以$P<0.05$为差异有统计学意义。

2 结 果

2.1 两组患者一般情况分析

表1结果表明,两组患者在年龄、身高、体质量、体表面积的差异均无统计学意义($P>0.05$)。

表1 两组患者一般情况分析

Table 1 General information analysis of the two groups ($n=30$)

Item	Group A	Group B
Age(years, $\bar{x}\pm s$)	72.24±3.94	71.86±4.09
Male[n(%)]	18(60.0)	17(56.7)
Height(m, $\bar{x}\pm s$)	1.61±0.87	1.64±0.65
Body mass(kg, $\bar{x}\pm s$)	56.88±5.62	59.10±7.12
Body surface area(m^2, $\bar{x}\pm s$)	1.70±0.65	1.73±0.45
Enneking stage ⅡA[n(%)]	17(56.7)	14(46.7)

Group A: received recombinant human thrombopoietin in the second chemotherapy cycle; Group B: received recombinant human thrombopoietin in the first chemotherapy cycle

2.2 两组患者化疗后血小板数量比较

两组患者在两个化疗周期的血小板最大值方面差异无统计学意义($P>0.05$)。两个周期内的用药组(Cycle 1:Group B;Cycle 2:Group A)与对照组(Cycle 1:Group A;Cycle 2:Group B)相比在血小板最低值提高明显,恢复时间及血小板≤50×10^9/L持续天数下降明显,差异有统计学意义($P<0.05$)。而血小板输注人次及数量方面用药组同样明显低于对照组,差异有统计学意义($P<0.05$;表2)。

2.3 两组患者两个化疗周期血小板数量自身比较

两组患者在两个化疗周期的自身对比如表3所示,两组患者用药周期(Group A:Cycle 2;Group B:Cycle 1)与对照周期相比(Group A:Cycle 1;Group B:Cycle 2),血小板最低值提高明显,血小板最大值差异无统计学意义($P>0.05$),恢复时间、血小板≤50×10^9/L持续天数、血小板输注人次及数量下降明显,差异有统计学意义($P<0.05$)。

2.4 两组患者应用重组人血小板生成素注射液后不良反应情况

两组共60例患者应用重组人血小板生成素注射液,其中发生发热2例,头晕1例,注射部位疼痛1例,共4例(6.7%),全部不良反应在对症治疗后缓解或消失。

3 讨 论

化疗作为针对恶性肿瘤患者的主要治疗方式,对大多数肿瘤的治疗效果已经得到肯定。但其疗效

表2 两组患者化疗后血小板数量比较

Table 2 Platelet counts analysis of the two groups after chemotherapy ($n=30$)

Cycle and Group	Minimal platelet count($\times10^9$/L)	Maximal platelet count($\times10^9$/L)	Recovery time(d)	Duration to platelet count≤50×10^9/L(d)	Platelet transfusion times (person-times)	Total platelet transfusion(U)
Cycle 1						
Group A	35.42±15.62	158.24±25.62	12.42±1.05	4.56±0.65	8	0.33±0.61
Group B	52.28±12.65*	160.42±38.24	6.82±0.68*	2.68±0.77*	2*	0.07±0.25*
Cycle 2						
Group A	48.66±12.68	155.42±40.93	7.56±0.46	2.28±1.05	2	0.10±0.31
Group B	34.83±10.34*	148.55±75.42	13.08±1.55*	4.65±1.12*	9*	0.37±0.61*

Group A: received recombinant human thrombopoietin in the second chemotherapy cycle; Group B: received recombinant human thrombopoietin in the first chemotherapy cycle. Compared with group A, *$P<0.05$

表3 两组患者两个化疗周期血小板数量自身比较

Table 3 Platelet counts analysis of the two groups between the two chemotherapy cycles ($n=30$)

Group and Cycle	Minimal platelet count($\times10^9$/L)	Maximal platelet count($\times10^9$/L)	Recovery time(d)	Duration to platelet count≤50×10^9/L(d)	Platelet transfusion times (person-times)	Total platelet transfusion(U)
Group A						
Cycle 1	35.42±15.62	158.24±25.62	12.42±1.05	4.56±0.65	8	0.33±0.61
Cycle 2	48.66±12.68*	155.42±40.93	7.56±0.46*	2.28±1.05*	2*	0.10±0.31*
Group B						
Cycle 1	52.28±12.65	160.42±38.24	6.82±0.68	2.68±0.77	2	0.07±0.25
Cycle 2	34.83±10.34*	148.55±75.42	13.08±1.55*	4.65±1.12*	9*	0.37±0.61*

Group A: received recombinant human thrombopoietin in the second chemotherapy cycle; Group B: received recombinant human thrombopoietin in the first chemotherapy cycle. Compared with cycle 1, *$P<0.05$

与化疗药物所用剂量成正比，未达到最佳剂量的化疗不但无法实现确切的治疗效果，还可能引起肿瘤组织的耐药继而导致化疗效果进一步降低。然而，大剂量化疗的风险主要为骨髓抑制，其中外周血血小板数量的减少直接导致患者出血风险增加，一旦发生则难以控制，甚至危及生命，老年患者尤为突出。重组人血小板生成素能够发挥与内源性血小板生成素相似的作用，提高外周血血小板的数量，减轻患者出血风险。本研究通过比较老年滑膜肉瘤患者化疗后应用重组人血小板生成素注射液对外周血血小板的效果，发现重组人血小板生成素注射液可以有效提高化疗患者血小板最低值，缩短恢复时间及血小板≤50×10^9/L的天数，并有效降低机采血小板的输注次数及人次，与国内外文献报道结果一致[8,9]。此外，其不良反应发生率较低，对症治疗后全部缓解同样符合相关报道[10,11]，在一定程度上证明了其安全性及适用性。

由于重组人血小板生成素是利用基因组织工程技术合成的，与内源性血小板生成素相比仍有一定的免疫原性，文献报道其在体内有诱导一过性抗体生成，但由于其抗体发生率与滴度较低，对重组人血小板生成素的促血小板作用无直接影响[12-14]。Li 等[15]则报道重组人血小板生成素抗体可引起患者产生血小板减少症状，尽管没有发生严重出血的情况，但3例患者全部出现了能与内源性血小板生成素发生交联反应的重组人血小板生成素抗体。本研究中未发现应用重组人血小板生成素后血小板仍持续降低的情况，且不良反应对症治疗后全部缓解或消失，可认为患者体内并未发生严重的免疫反应，但针对使用重组人血小板生成素后血小板仍无上升趋势的患者，应积极检查其血清内是否产生能够与内源性血小板生成素发生交联反应的抗体，若发生，则需尽早停止使用重组人血小板生成素以减轻免疫反应的程度。

综上所述，重组人血小板生成素可以有效提高化疗患者外周血血小板数量，保证患者能够接受最优化疗剂量，加速患者血小板恢复，减少血小板输注人次及数量，其不良反应少，安全性及可靠性良好，值得在临床上应用。

【参考文献】

[1] Weiss SW, Goldblum JR. Enzinger and Weiss's Soft Tissue Tumors[M]. 5th ed. St Louis: Mosby, 2008: 769-771.

[2] Lewis JJ, Antonescu CR, Leung DH, *et al*. Synovial sarcoma: a multivariate analysis of prognostic factors in 112 patients with primary localized tumors of the extremity[J]. J Clin Oncol, 2000, 18(10): 2087-2094.

[3] Tanaka K, Mizusawa J, Fukuda H, *et al*. Perioperative chemotherapy with ifosfamide and doxorubicin for high-grade soft tissue sarcomas in the extremities (JCOG0304)[J]. Jpn J Clin Oncol, 2015, 45(6): 555-561.

[4] Ferrari A, De Salvo GL, Brennan B, *et al*. Synovial sarcoma in children and adolescents: the European Pediatric Soft Tissue Sarcoma Study Group prospective trial (EpSSG NRSTS 2005)[J]. Ann Oncol, 2015, 26(3): 567-572.

[5] Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy[J]. Oncology (Williston Park), 2015, 29(4): 282-294.

[6] Wang H, Dong Q, Fu R, *et al*. Recombinant human thrombopoietin treatment promotes hematopoiesis recovery in patients with severe aplastic anemia receiving immunosuppressive therapy[J]. Biomed Res Int, 2015, 2015: 597293.

[7] Hitchcock IS, Kaushansky K. Thrombopoietin from beginning to end[J]. Br J Haematol, 2014, 165(2): 259-268.

[8] Angiolillo AL, Davenport V, Bonilla MA, *et al*. A phase I clinical, pharmacologic, and biologic study of thrombopoietin and granulocyte colony-stimulating factor in children receiving ifosfamide, carboplatin, and etoposide chemotherapy for recurrent or refractory solid tumors: a Children's Oncology Group experience[J]. Clin Cancer Res, 2005, 11(7): 2644-2650.

[9] Parameswaran R, Lunning M, Mantha S, *et al*. Romiplostim for management of chemotherapy-induced thrombocytopenia[J]. Support Care Cancer, 2014, 22(5): 1217-1222.

[10] Newland A. Thrombopoietin receptor agonists in the treatment of thrombocytopenia[J]. Curr Opin Hematol, 2009, 16(5): 357-364.

[11] Kuter DJ. Thrombopoietin and thrombopoietin mimetics in the treatment of thrombocytopenia[J]. Annu Rev Med, 2009, 60: 193-206.

[12] Basser RL, O'Flaherty E, Green M, *et al*. Development of pancytopenia with neutralizing antibodies to thrombopoietin after multicycle chemotherapy supported by megakaryocyte growth and development factor[J]. Blood, 2002, 99(7): 2599-2602.

[13] Carpenedo M, Cantoni S, Coccini V, *et al*. Response loss and development of neutralizing antibodies during long-term treatment with romiplostim in patients with immune thrombocytopenia: a case series[J]. Eur J Haematol, 2015, Dec 31. [Epub ahead of print]

[14] Vadhan-Raj S. Clinical findings with the first generation of thrombopoietic agents[J]. Semin Hematol, 2010, 47(3): 249-257.

[15] Li J, Yang C, Xia Y, *et al*. Thrombocytopenia caused by the development of antibodies to thrombopoietin[J]. Blood, 2001, 98(12): 3241-3248.

（编辑：周宇红）