

来那度胺对多发性骨髓瘤患者自体移植造血干细胞采集影响

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[摘要] 目的 探讨来那度胺对多发性骨髓瘤(MM)患者自体移植造血干细胞采集的影响。方法 回顾性分析北部战区总医院血液科 2015—2020 年采集外周血造血干细胞移植的 42 例 MM 患者的临床资料。按照年龄将患者分为年龄 ≤ 60 岁组($n=24$)与年龄 >60 岁组($n=18$)。按照化疗疗程数将患者分为疗程 <6 次组($n=27$)和疗程 ≥ 6 次组($n=15$)。比较两种化疗方案对造血干细胞采集的影响时,选取我院 2018—2020 年收治的 32 例 MM 患者为研究对象,并根据不同方案将其分为来那度胺、硼替佐米及地塞米松(RVD)组($n=10$)与硼替佐米、环磷酰胺及地塞米松(BCD)组($n=22$)。分析年龄、动员前化疗方案、动员前化疗疗程数与造血干细胞采集间的关系。结果 RVD 组患者单个核细胞、CD34+ 细胞、首次采集成功率均低于 BCD 组,差异均有统计学意义($P<0.05$)。年龄 >60 岁组患者首次采集 CD34+ 细胞计数低于年龄 ≤ 60 岁组,差异有统计学意义($P<0.05$)。疗程 <6 次组患者首次采集 CD34+ 细胞计数高于疗程 ≥ 6 次组,差异有统计学意义($P<0.05$)。结论 含有来那度胺的化疗方案会损伤造血干细胞,增加造血干细胞采集难度,尤其对于年龄 >60 岁患者,动员前含有来那度胺的化疗方案应慎用。动员前化疗疗程数应适中,过多的化疗会损害造血干细胞。

[关键词] 来那度胺; 多发性骨髓瘤; 自体移植造血干细胞

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Effect of lenalidomide on hematopoietic stem cell collection for autologous transplantation in patients with multiple myeloma

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Abstract: Objective To investigate the effect of lenalidomide on hematopoietic stem cell collection for autologous transplantation in patients with multiple myeloma(MM). **Methods** A retrospective study was performed on 42 cases of patients with MM who were admitted and underwent lenalidomide on hematopoietic stem cell collection for autologous transplantation who were admitted from 2015 to 2020. According to their age, the patients were divided into the group ≤ 60 years old($n=24$) and group >60 years old($n=18$). According to the number of chemotherapy courses, the patients were divided into two groups: treatment <6 times group($n=27$) and treatment ≥ 6 times group($n=15$). When comparing the effects of two chemotherapy regimens on hematopoietic stem cell collection, 32 MM patients who were admitted from 2018 to 2020 were selected as the research objects, and according to different regimens, patients were divided into lenalidomide, bortezomib and dexamethasone(RVD) group($n=10$) and bortezomib, cyclophosphamide and dexamethasone(BCD) group($n=22$). The relationship between age, chemotherapy regimens before mobilization, the number of chemotherapy courses before mobilization and hematopoietic stem cell collection was analyzed. **Results** The mononuclear cells, CD34+ cells and the first collection success rate in RVD group were lower than those in BCD group, and the differences were statistically significant($P<0.05$). The number of CD34+ cells collected for the first time in the age >60 years group was lower than that in the age ≤ 60 years group($P<0.05$). The number of CD34+ cells collected for the first time in the treatment >6 times group was higher than that in the treatment ≥ 6 times group($P<0.05$). **Conclusion** Chemotherapy regimens containing lenalidomide will damage hematopoietic stem cells and increase the difficulty of hematopoietic stem cell collection. Especially for patients aged >60 years, chemotherapy regimens containing lenalidomide before mobilization should be used with caution. The number of chemotherapy courses before mobilization should be moderate. Excessive chemotherapy will damage hematopoietic stem cells.

Key words: Lenalidomide; Multiple myeloma; Autologous transplantation of hematopoietic stem cells

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多发性骨髓瘤(multiple myeloma, MM)是血液系统常见的恶性克隆性浆细胞疾病,好发于老年人。随着新药时代的到来,免疫调节剂及蛋白酶体

抑制剂可加大 MM 患者的缓解深度,使得微小残留病变(minimal residual disease, MRD)阴性率进一步提高。患者的总生存期得以延长^[1]。有研究表明,来那度胺、硼替佐米及地塞米松(lenalidomide, bortezomib and dexamethasone, RVD)方案诱导治疗 MM 患者后 MRD 阴性率较高,但是联合自体造血干细胞移植后 MRD 阴性率更高^[2],自体造血干细胞移植依然是 MM 患者治疗中的重要组成部分。来那度胺对骨髓具有抑制作用,但对 MM 患者外周血造血干细胞采集之间是否存在影响,需进一步观察研究。本研究回顾性分析了 42 例 MM 患者的自体干细胞移植的临床资料,旨在探讨含来那度胺的化疗方案对 MM 患者自体移植造血干细胞采集的影响。现报道如下。

1 资料与方法

1.1 一般资料 选取北部战区总医院血液科 2015—2020 年接受自体造血干细胞移植的 42 例 MM 患者为研究对象。纳入标准:符合 MM 诊断标准;具有自体造血干细胞移植适应证。排除标准:自身因素导致的采集失败者;疾病终末期者。其中,男性 23 例,女性 19 例;年龄 41~68 岁,平均年龄 57 岁。比较 RVD 与硼替佐米、环磷酰胺及地塞米松(bortezomib cyclophosphamide and dexamethasone, BCD)化疗方案对造血干细胞采集的影响时,选取我院 2018—2020 年收治的 32 例 MM 患者为研究对象,并根据不同方案将其分为 RVD 组($n=10$)与 BCD 组($n=22$)。按照年龄将患者分为年龄 ≤ 60 岁组($n=24$)与年龄 >60 岁组($n=18$)。按照化疗疗程数将患者分为疗程 <6 次组($n=27$)和疗程 ≥ 6 次组($n=15$)。本研究经医院伦理委员会批准。患者均签署知情同意书。

1.2 研究方法 分别统计患者年龄、性别、疾病类

型、细胞遗传学、疾病状态、动员前化疗方案、动员前化疗疗程数、单个核细胞计数、CD34+细胞计数及首次采集成功比例。首次采集数是指第 1 次动员后的第 1 天采集数量,包括单个核细胞和 CD34+细胞。分析年龄、动员前化疗方案、动员前化疗疗程数与造血干细胞采集间的关系。42 例患者均采用大剂量的环磷酰胺联合粒细胞刺激因子进行外周血干细胞动员。环磷酰胺剂量为 3 g/m^2 ,分 2 d 给药,同时进行美司钠解救治疗。化疗后,患者白细胞低点拐点处开始给予粒细胞刺激因子 $10 \mu\text{g}/(\text{kg}\cdot\text{d})$ 皮下注射至干细胞采集。当患者白细胞升至 4×10^9 个/L 以上时,采用梯度离心的方法分离外周血单个核细胞,并计算 CD34+细胞数值。采集成功的指征为 CD34+细胞 $\geq 2\times 10^6$ 个/kg。造血重建判断标准:无血小板输注情况下,血小板计数连续 7 d $>20.0\times 10^9$ 个/L 为血小板植入;无粒细胞刺激因子治疗的情况下,中性粒细胞计数连续 2 d $>0.5\times 10^9$ 个/L 为中性粒细胞植入。

1.3 统计学方法 采用 SPSS 25.0 统计学软件对数据进行处理。计量资料用均数 $\pm$ 标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验。计数资料用例(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 动员前化疗方案对造血干细胞采集及植入影响 RVD 组患者单个核细胞、CD34+细胞、首次采集成功率均低于 BCD 组,差异均有统计学意义($P<0.05$)。见表 1。BCD 组中 4 例患者植入情况因记录不详而导致资料缺失,1 例移植期间感染明显影响植入排除。RVD 组患者中性粒细胞植入与血小板植入时间均大于 BCD 组,差异均有统计学意义($P<0.05$)。见表 2。

表 1 动员前化疗方案对 MM 患者造血干细胞采集的影响($\bar{x}\pm s$)

组别	单个核细胞/个 $\cdot\text{kg}^{-1}$	CD34+细胞/个 $\cdot\text{kg}^{-1}$	首次采集成功/例(百分率/%)
RVD 组($n=10$)	$(2.94\pm 1.22)\times 10^8$	$(1.47\pm 0.91)\times 10^6$	3(30.00)
BCD 组($n=22$)	$(3.30\pm 2.07)\times 10^8$	$(5.46\pm 6.79)\times 10^6$	16(94.12)
P 值	<0.05	<0.05	<0.05

2.2 年龄对造血干细胞采集的影响 年龄 >60 岁患者首次采集 CD34+细胞计数低于年龄 ≤ 60 岁组,差异有统计学意义($P<0.05$)。两组患者单个核细胞计数与首次采集成功率比较,差异均无统计学意义($P>0.05$)。见表 2。

2.3 动员前化疗疗程数对造血干细胞采集的影响 疗程 <6 次组患者首次采集 CD34+细胞计数高于疗程 ≥ 6 次组,差异有统计学意义($P<0.05$)。两组患者单个核细胞计数与首次采集成功率比较,差异均无统计学意义($P>0.05$)。见表 3。

3 讨论

多项研究表明,来那度胺是造血干细胞采集的危险因素,可以抑制骨髓和改变基质环境,进而影响造血干细胞采集成功率^[3]。在新药时代,大量的靶向治疗药物被应用于 MM 临床救治,但是自体造血干细胞移植仍然是一线治疗方法^[4]。在方案选择

表 2 动员前化疗方案对 MM 患者造血干细胞植入的影响($\bar{x} \pm s$, μ)

组别	中性粒细胞植入	血小板植入
RVD 组	12.30 $\pm$ 1.06	14.00 $\pm$ 1.15
BCD 组	10.65 $\pm$ 0.79	11.59 $\pm$ 1.06
P 值	<0.05	<0.05

表 3 年龄对 MM 造血干细胞采集影响($\bar{x} \pm s$)

组别	单个核细胞/个 $\cdot$ kg ⁻¹	CD34+细胞/个 $\cdot$ kg ⁻¹	首次采集成功/例(百分率/%)
年龄 $\leq$ 60 岁组($n=24$)	(3.75 $\pm$ 1.80) $\times 10^8$	(4.87 $\pm$ 6.73) $\times 10^6$	14(58.33)
年龄>60 岁组($n=18$)	(2.79 $\pm$ 1.65) $\times 10^8$	(1.85 $\pm$ 1.10) $\times 10^6$	7(38.89)
P 值	>0.05	<0.05	>0.05

表 4 采干前化疗程数对 MM 造血干细胞采集的影响($\bar{x} \pm s$)

组别	单个核细胞/个 $\cdot$ kg ⁻¹	CD34+细胞/个 $\cdot$ kg ⁻¹	首次采集成功/例(百分率/%)
疗程<6 次组($n=27$)	(3.31 $\pm$ 1.94) $\times 10^8$	(4.57 $\pm$ 6.37) $\times 10^6$	15(55.56)
疗程 $\geq$ 6 次组($n=15$)	(3.39 $\pm$ 1.50) $\times 10^8$	(1.80 $\pm$ 1.39) $\times 10^6$	6(40.00)
P 值	>0.05	<0.05	>0.05

时需考虑对造血干细胞采集的影响。自体移植成功的前提就是造血干细胞的成功采集。有研究显示,普乐沙福动员方案可弥补来那度胺对造血干细胞的损耗,提高采集效益^[5-6],但价格昂贵,受到多方面限制。Dosani 等^[6]研究表明,来那度胺的使用可导致髓系和红系祖细胞降低。Zheng 等^[7]研究显示 4 例以来那度胺采集 CD34+细胞患者均失败,表明来那度胺的使用是造血干细胞采集的不利因素($P<0.05$)。有研究显示,来那度胺抑制骨髓是通过诱导毒性 T 细胞和 NK 细胞产生干扰素- γ 进而发挥作用^[8]。国外多项研究表明,来那度胺的使用可增加造血干细胞采集的失败率,CD34+细胞数下降^[9-10],与本研究结果一致。目前建议使用来那度胺化疗方案的患者在前 4 个周期内即行干细胞采集术,并应尽可能与造血干细胞采集间留有足够的药物洗脱期,以供患者机体的恢复^[11-12]。

有研究显示,输注 CD34+细胞数越充足,患者移植后血小板的长期恢复情况就越好,需要输血的概率越小,可使患者获得的较长总生存时间,但与 1 年生存率无关^[13]。本研究结果显示,RVD 组患者单个核细胞、CD34+细胞、首次采集成功率均低于 BCD 组,差异均有统计学意义($P<0.05$)。这一结果表明,细胞植入越早,发生并发症概率越小,能进一步降低医疗及护理成本。本研究结果还显示,年龄 $\leq$ 60 岁组患者首次采集 CD34+细胞计数低于年

龄 $\leq$ 60 岁组,差异有统计学意义($P<0.05$),与国内外研究结果一致^[6,14]。随着年龄的增长,身体机能发生不可逆性的退化,这提示对于 60 岁以上患者更应该重视临床治疗方案的使用,尽量避免不利因素对造血干细胞采集的影响,应慎重选择。本研究结果显示,疗程<6 次组患者首次采集 CD34+细胞计数高于疗程 $\geq$ 6 次组,差异有统计学意义($P<0.05$)。疗程 $\geq$ 6 次患者干细胞损害较大,获得的 CD34+细胞数量较少。笔者认为,任何化疗均不可避免对造血干细胞产生影响。有研究显示,沙利多胺可降低约 10% 的干细胞产量,同时硼替佐米也是导致造血干细胞的产量下降的原因^[15]。

综上所述,含有来那度胺的化疗方案会损伤造血干细胞,增加造血干细胞采集难度,尤其对于年龄>60 岁患者,动员前含有来那度胺的化疗方案应慎用。动员前化疗疗程数应适中,过多的化疗会损害造血干细胞。治疗期间,应尽量避免不利因素对采集干细胞能力的影响。

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