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高三尖杉酯碱联合阿糖胞苷治疗骨髓增生异常综合征的疗效及安全性分析 *

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摘要 目的:探讨高三尖杉酯碱联合阿糖胞苷治疗骨髓增生异常综合征的疗效及安全性。**方法:**选择 2015 年 1 月 -2019 年 1 月在我院接受治疗的 40 例骨髓增生异常综合征患者,采用抽签法分为观察组(n=21)和对照组(n=19)。两组均给予地西他滨治疗,对照组在此基础上给予阿糖胞苷治疗,观察组在对照组的基础上给予高三尖杉酯碱治疗。比较两组患者的临床缓解情况、治疗前后血清内皮生长因子(VEGF)、骨髓中原始细胞占比、白细胞介素 6(IL-6)、白细胞介素 10(IL-10)、肿瘤坏死因子(TNF-α)水平、生存质量评分的变化及并发症的发生情况。**结果:**治疗后,两组总缓解率分别为 71.43%,36.84%,观察组显著高于对照组(P<0.05);两组血清 VEGF、骨髓中原始细胞占比水平均较治疗前显著降低,且观察组上述指标均明显低于对照组(P<0.05);两组血清 IL-6、TNF-α 水平均较治疗前显著降低,IL-10 较治疗前显著升高, 且观察组血清 IL-6、TNF-α 水平均显著低于对照组,IL-10 水平明显高于对照组(P<0.05);两组生存质量评分水平均较治疗前显著降低,且观察组明显低于对照组(P<0.05);两组并发症总发生率为 52.38%、84.21%,观察组显著低于对照组(P<0.05)。**结论:**高三尖杉酯碱联合阿糖胞苷治疗骨髓增生异常综合征的效果显著优于单用阿糖胞苷治疗,其可有效改善患者生存质量水平,且安全性更高,可能与其降低血清 IL-6、TNF-α 水平,升高 IL-10 水平,减轻炎症反应有关。

关键词:高三尖杉酯碱;阿糖胞苷;骨髓增生异常综合征;安全性

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Efficacy and Safety of Cytarabine Combined with Cytarabine in the Treatment of Myelodysplastic Syndrome*

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ABSTRACT Objective: To study the efficacy and safety of cytarabine combined with cytarabine in the treatment of myelodysplastic syndrome. **Methods:** 40 patients with myelodysplastic syndrome who were treated in our hospital from January 2015 to January 2019 were selected and randomly divided into the observation group (n=21) and the control group (n=19). Both groups were treated with decitabine, the control group was additionally treated with cytarabine, and the observation group was treated with trigeminine on the basis of control group. The clinical remission, changes of serum endothelial growth factor (VEGF), proportion of primary cells in bone marrow, interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor (TNF)-α, quality of life score before and after treatment and incidence of complications were compared between the two groups. **Results:** After treatment, the total remission rate of observation group and control group were 71.43% and 36.84% respectively, which was significantly higher in the observation group than that in the control group (P<0.05). The proportion of serum VEGF and primitive cells in bone marrow in both groups was significantly lower than that before treatment, and the above indexes in the observation group were significantly lower than those in the control group (P<0.05). The serum IL-6 and TNF-α levels in both groups were significantly lower than those before treatment, which was significantly higher in the observation group. The serum IL-10 levels in the observation group were significantly higher than those in the control group, which was significantly higher in the observation group than those in the control group (P<0.05). The score of quality of life in both groups was significantly lower than that before treatment, which was significantly lower in the observation group than that of the control group (P<0.05). The total incidence of complications in the two groups was 52.38% and 84.21%, which was significantly lower in the observation group than in the control group (P<0.05). **Conclusion:** Monotherapy with cytarabine and trigeminine is more effective in the treatment of myelodysplastic syndrome than cytarabine alone, which can effectively improve the patients' quality of life with higher safety. The underlying mechanisms may be related to the decrease of serum IL-6 and TNF-α levels and the increase of IL-10 levels.

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前言

骨髓增生异常综合征是一种恶性血液病，常见于老年人，由一组异质性较强的疾病组成，是由于造血干细胞水平损伤而产生的克隆性疾病，临床现为乏力、呼吸困难及造血功能衰竭等症状，严重影响患者的生活质量[1,2]。骨髓增生异常综合征发病男性多于女性，超额病死率占全因病死率的 3/4，可能是因为患者多集中在中老年人，并发症较多，预后多于骨髓原始细胞比例和细胞遗传学异常有关[3]。

目前，异基因造血干细胞移植是唯一可能治愈该病的治疗方法，但其受到患者体内细胞遗传学的影响，远期预后不确定[4]。阿糖胞苷是一种嘧啶类抗代谢药物，被广泛运用于骨髓增生异常综合征、急性白血病等疾病中，但该药单一治疗效果一般，需与其他药物联合治疗以提高治疗效果[5,6]。高三尖杉酯碱是一种细胞周期特异性的生物碱，能诱导细胞分化，抑制糖蛋白合成[7]。本研究主要探讨了高三尖杉酯碱联合阿糖胞苷治疗骨髓增生异常综合征的疗效及安全性，现报道如下。

1 资料与方法

1.1 一般资料

选择 2015 年 1 月 -2019 年 1 月在我院接受治疗的 40 例骨髓增生异常综合征患者。采用抽签法分为两组，观察组 21 例，包括男 12 例，女 9 例，年龄 34-66 岁，平均(49.63± 4.13)岁，疾病类型：难治性血细胞减少伴单系增生异常 13 例、难治性血细胞减少伴多系增生异常 7 例、难治性血细胞减少伴铁粒幼细胞增多 1 例；对照组 19 例，包括男 12 例，女 7 例，年龄 35-65 岁，平均(49.61± 4.14)岁，疾病类型：难治性血细胞减少伴单系增生异常 11 例、难治性血细胞减少伴多系增生异常 6 例、难治性血细胞减少伴铁粒幼细胞增多 2 例。两组基线资料比较无明显差异(P>0.05)，具有可比性。

骨髓增生异常综合征的诊断参照《骨髓增生异常综合征诊断与治疗中国专家共识》[8]，(1)持续 1 系或者多系血细胞减少；(2)骨髓涂片中红细胞系中发育异常细胞≥ 10%；(3)检查骨髓细胞表型异常；(4)骨髓增生异常综合征常见染色体异常。纳入标准：(1)符合上述诊断标准；(2)临床资料完整；(3)未经化疗者；(4)病情稳定，无生命危险；(5)签署知情同意书。排除标准：(1)重症有生命危险患者；(2)患有意识障碍、精神障碍者；(3)合并恶性肿瘤者；(4)妊娠期患者；(5)合并其他血液疾病者；(6)依从性较差者；(7)对本次研究药物过敏者。

1.2 治疗方法

两组均给予地西他滨(规格：50 mg，生产厂家：山东新时代药业有限公司，国药准字 H20123294)25 mg/m^2 皮下注射，1 h 1 d。对照组给予阿糖胞苷(规格：1 mL：0.1 g，生产厂家：F. H. Faulding & Co.Ltd.Trading as David Bull Lab.，国药准字：X20010086)10 mg/m^2，皮下注射，每 12 h 1 次。观察组在对照组的基础上加用高三尖杉酯碱(规格：15 mg；生产厂家：浙江大冢制药有限公司；国药准字 H20110115)10 mg/m^2 皮下注射，1 d 1次。

1.3 观察指标

采集空腹静脉血 5 mL，以 3000 r·min^{-1} 的速度进行离心，时间 10 min，提取上层血清后，置于零下 20℃的冷冻箱内存储以备检测，采用双抗体夹心酶联免疫吸附法测定 VEGF、IL-6、IL-10、TNF-α 水平；记录治疗前后骨髓中原始细胞占比；采用 EORTC QLQ-C30 量表评定患者生存质量；记录并发症的发生情况。疗效评定标准：完全缓解：临床症状消失，骨髓原始细胞≤ 5%；部分缓解：临床症状改善，骨髓原始细胞≥ 50%；未缓解：临床症状无明显改善甚至加重。

1.4 统计学分析

以 SPSS 18.0 软件包处理实验数据，符合正态分布计量资料用均数± 标准差($\bar{x}$± s)表示，组间比较使用独立样本 t 检验，计数资料以率表示，组间比较采用 x^2 检验，以 P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后，两组总有缓解率分别为 71.43%，36.84%，观察组显著高于对照组(P<0.05)，见表 1。

表 1 两组临床疗效的比较[例(%)]

Table 1 Comparison of the efficacy between the two groups[n(%)]

Groups	n	Complete response	Partial remission	No remission	Total remission rate
Observation group	21	2(9.52)	13(61.90)	6(28.57)	15(71.43)
Control group	19	1(5.26)	6(31.58)	12(63.16)	7(36.84)
x^2 value					4.821
P value					0.028

2.2 两组治疗前后血清 VEGF 水平、骨髓中原始细胞占比的比较

治疗前，两组血清 VEGF 水平、骨髓中原始细胞占比水平比较无明显差异(P>0.05)；治疗后，两组血清 VEGF 水平、骨髓中原始细胞占比水平均较治疗前显著降低，且观察组上述指标均显著低于对照组(P<0.05)，见表 2。

2.3 两组治疗前后血清 IL-6、IL-10、TNF-α 水平的比较

治疗前，两组血清 IL-6、IL-10、TNF-α 水平比较无明显差

异；治疗后，两组血清 IL-6、TNF-α 水平均较治疗前显著降低，血清 IL-10 水平较治疗前显著升高，且观察组血清 IL-6、TNF-α 水平均显著低于对照组，血清 IL-10 水平显著高于对照组（$P<0.05$），见表 3。

表 2 两组治疗前后血清 VEGF 水平、骨髓中原始细胞占比的比较（$\bar{x}\pm s$）

Table 2 Comparison of the serum levels of VEGF and proportion of bone marrow primordial cells between the two groups before and after treatment（$\bar{x}\pm s$）

Groups	n	VEGF(ng/L)		Proportion of primordial cells in bone marrow(%)	
		Beforetreatment	After treatment	Beforetreatment	After treatment
Observation group	21	212.63± 23.14	127.56± 15.47	10.18± 5.12	5.13± 2.21
Control group	19	214.12± 23.43	153.36± 18.61	10.22± 5.32	7.59± 3.40
t value		0.202	4.785	0.024	2.739
P value		0.841	0.000	0.981	0.009

表 3 两组治疗前后血清 IL-6、IL-10、TNF-α 水平的比较（$\bar{x}\pm s$）

Table 3 Comparison of the serum IL-6, IL-10, and TNF-α levels between the two groups before and after treatment（$\bar{x}\pm s$）

Groups	n	IL-6(pg/mL)		IL-10(pg/mL)		TNF-α(ng/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	21	45.78± 7.21	34.26± 6.21	8.05± 3.23	15.35± 4.23	1.35± 0.31	0.91± 0.13
Control group	19	45.71± 7.23	39.98± 6.56	8.11± 3.21	10.32± 2.34	1.37± 0.32	1.05± 0.12
t value		0.031	2.832	0.059	4.584	0.201	3.527
P value		0.976	0.007	0.953	0.000	0.842	0.001

2.4 两组治疗前后生存质量评分的比较

治疗前，两组生存质量评分比较无明显差异（$P>0.05$）；治疗后，两组生存质量评分均交治疗前显著降低，且观察组明显低于对照组（$P<0.05$）。

3 讨论

骨髓增生异常综合征的主要特征为无效造血导致血细胞减少，部分患者可发展为急性髓系白血病[9]。其发病机制较为复杂，可能涉及细胞分化和和凋亡异常、细胞免疫功能异常及造血调控因子异常等。研究显示骨髓增生异常综合征发病率可随着年龄的增长而升高，已成为老年人最常见的血液系统恶性疾病[10,11]。因此，对骨髓增生异常综合征患者及时有效治疗具有重要意义。临床治疗骨髓增生异常综合征以阿糖胞苷为主，阿糖胞苷是嘧啶类抗代谢药物，可诱导肿瘤细胞分化，但该药小剂量效果不佳，加大剂量时可诱导患者肝肾等重要器官功能下降，导致患者耐受性较差，病死率较高，部分患者可因为不耐受化疗毒性及不良反应而放弃治疗[12-14]。

高三尖杉酯碱是 20 世纪 70 年代首先从同属植物提取得到的一种生物碱，可通过线粒体膜电位下降和半胱氨酸天冬酶 3 激活而诱导细胞凋亡，诱导内皮细胞凋亡而抑制其增殖，既有细胞毒作用，又有诱导分化作用[15-17]。有研究显示高三尖杉酯碱在骨髓增生异常综合征的治疗中具有较好的效果，且价廉易得，对减轻患者的经济负担也有一定意义[18]。本研究结果显示联合高三尖杉酯碱治疗的患者总有缓解率分别为 71.43%，明显高于对照组的患者，且并发症总发生率为 52.38%，也低于对照组患者，提示高三尖杉酯碱联合阿糖胞苷可提高骨髓增生异常综合征的治疗效果，降低并发症发生率。分析其原因可能是因为高三尖杉酯碱可减轻对骨髓造血细胞的抑制作用，心脏毒副反应和胃肠道反应较小。

大量研究表明血管新生是肿瘤发生和进展的重要基础之一，骨髓增生异常综合征也伴有血管新生[19,20]。VEGF 是促使血管新生的一个重要因子，骨髓增生异常将扰乱血管生成的抑制因子和刺激因子，造成 VEGF 过度增加。VEGF 是一个主要的存活或抗凋亡因子，具有多种生物学功能，能增强血管渗透性，引起血管增生，同时还能刺激内皮细胞增生并促进血管形成，参与血管外基质重塑[21-23]。本研究结果显示观察组治疗后血清 VEGF、骨髓中原始细胞占比水平均显著低于对照组，提示高三尖杉酯碱联合阿糖胞苷可有效改善骨髓抑制，恢复造血功能，提高自身机体免疫力及抗肿瘤能力，改善患者病情。分析其原因可能是因为阿糖胞苷是嘧啶类抗代谢药物，可诱导肿瘤细胞分化及白血病细胞凋亡，而高三尖杉酯碱则能对骨髓造血细胞有全面抑制作用，可抑制粒细胞系列，诱导原发性髓系白血病细胞凋亡，同时诱导白血病细胞进入分化状态，减轻骨髓造血细胞的抑制，同时可诱导多种恶性肿瘤细胞系中的细胞有效的敏化作用，促进肿瘤细胞坏死，二者可起到协同诱导肿瘤细胞凋亡作用。

近年来研究表明造血调控因子紊乱是骨髓增生异常综合征发生的主要原因，而骨髓内的炎症反应与骨髓增生异常综合征产生的免疫损伤有关，可造成造血细胞损伤[24-26]。IL-6 是判断患者病情变化的参考指标；IL-10 是公认的炎症与免疫抑制因子，又称细胞因子合成抑制因子和 B 淋巴细胞衍生细胞生长因子，对造血系统、心血管系统等十分重要，可通过与其受体结合而产生免疫反应，抑制 T 淋巴细胞，诱导 T 淋巴细胞对抗原的免疫耐受，同时可促进肿瘤生长，抑制细胞凋亡，调节肿瘤微

环境[27,28]。有研究显示骨髓增生异常综合征患者免疫功能异常，且可随着疾病发展使免疫功能紊乱加剧，IL-10 可拮抗造血负调控因子的表达，其水平升高与骨髓增生异常综合征转化有关，在骨髓增生异常综合征中发挥造血调控因子的作用。TNF-α 主要由巨噬细胞产生，是一种促凋亡因子，可通过上调 Fas 而诱导凋亡。有研究显示骨髓增生异常综合征形成与过度凋亡有关，且 TNF-α 抑制剂可改善骨髓增生异常综合征患者的骨髓无效造血。本研究结果显示高三尖杉酯碱联合阿糖胞苷的患者血清 IL-6、TNF-α 水平均低于对照组，而血清 IL-10 明显升高，提示联合治疗可改善骨髓增生异常综合征炎症因子水平。分析其原因可能是因为高三尖杉酯碱可通过调节骨髓造血微环境，减少机体骨髓内免疫因子介导的炎症反应，从而降低炎症因子水平。此外，观察组治疗后生存质量评分较对照组显著降低，Nobuhiro Hirasawa[29]等研究显示高三尖杉酯碱联合阿糖胞苷在骨髓增生异常综合征的治疗中效果显著，可改善患者临床症状，提高患者的生活质量。

综上所述，高三尖杉酯碱联合阿糖胞苷治疗骨髓增生异常综合征的效果显著优于单用阿糖胞苷治疗，其可有效改善患者生存质量水平，且安全性更高，可能与其降低血清 IL-6、TNF-α 水平，升高 IL-10 水平，减轻炎症反应有关。

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