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参芪扶正注射液联合地西他滨对急性髓系白血病患者血清 HGF、VEGF 与 LDH 水平的影响 *

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摘要 目的:探讨参芪扶正注射液联合地西他滨对急性髓系白血病患者血清肝细胞生长因子(HGF)、血管内皮生长因子(VEGF)与乳酸脱氢酶(LDH)水平的影响。**方法:**选择 2014 年 8 月至 2016 年 8 月我院接诊的 84 例急性髓系白血病患者,通过随机数表法分为观察组(n=42)和对照组(n=42)。对照组给予地西他滨+DA 化疗方案(柔红霉素+阿糖胞苷),观察组联合参芪扶正注射液,两组均以 21d 为 1 个周期,连续治疗 2 个周期。比较两组治疗前后血常规、血清 HGF、VEGF 和 LDH 水平的变化、临床疗效及不良反应的发生情况。**结果:**治疗后,两组血常规、血清 HGF、VEGF 和 LDH 水平均较治疗前显著改善($P<0.05$);观察组白细胞计数(WBC)明显低于对照组,血红蛋白(HGB)、血小板计数(PLT)、中性粒细胞计数(NEU)水平明显高于对照组($P<0.05$);观察组临床疗效总缓解率明显高于对照组($P<0.05$);观察组恶心呕吐、感染、多汗、出血、心脏毒性发生率均明显低于对照组($P<0.05$)。**结论:**应用参芪扶正注射液联合地西他滨治疗急性髓系白血病患者临床效果显著,有助于降低毒副反应,其内在机制可能和降低血清 HGF、VEGF、LDH 的水平相关。

关键词:急性髓系白血病;地西他滨;参芪扶正注射液;肝细胞生长因子;血管内皮生长因子;乳酸脱氢酶

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Effect of Shenqi Fuzheng Injection Combined with Decitabine on the Serum HGF, VEGF and LDH Levels of Patients with Acute Myeloid Leukemia*

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ABSTRACT Objective: To study the clinical efficacy of shenqi fuzheng injection combined with decitabine on the acute myeloid leukemia and its effects on hepatocyte growth factor(HGF), vascular endothelial growth factor(VEGF) and lactate dehydrogenase(LDH). **Methods:** 84 patients of acute myeloid leukemia who received therapy from August 2014 to August 2016 in our hospital were selected. According to random number table, those patients were divided into the observation group (n=42) and the control group (n=42). The control group was treated with decitabine+ DA chemotherapy regimen (Daunorubicin + cytarabine), while the observation group was combined with shenqi fuzheng injection, both groups were treated with 21d for 1 cycles, continuous treatment for 2 cycles. The changes of blood routine, serum HGF, VEGF and LDH levels before and after treatment and the clinical efficacy and incidence of adverse reactions were compared between the two groups. **Results:** After treatment, the routine blood routine, serum HGF, VEGF and LDH levels of the two groups were significantly improved($P<0.05$); the white blood count (WBC) of observation group was significantly lower than that of the control group, and the hemoglobin (HGB), platelet count (PLT) and neutrophil count (NEU) were significantly higher than that of the control group ($P<0.05$); the total remission rate of clinical efficacy of observation group were significantly higher than that of the control group ($P<0.05$); the incidence of nausea and vomiting, infected, hyperhidrosis, hemorrhage, cardiotoxicity in the observation group were significantly lower than those of the control group($P<0.05$). **Conclusion:** Shenqi fuzheng injection combined with decitabine is effective for acute myeloid leukemia, which can improve the clinical efficacy and reduce the toxic and side effects, and it's intrinsic mechanism may be related to the decrease of serum HGF, VEGF and LDH levels.

Key words: Acute myeloid leukemia; Decitabine; Shenqi Fuzheng Injection; Hepatocyte growth factor; Vascular endothelial growth factor; Lactate dehydrogenase

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前言

急性髓系白血病是一种常见的急性白血病类型,近年来其发病率呈日趋增高的现象^[1]。对此类患者的唯一治愈手段是异基因造血干细胞移植,但由于经济条件、干细胞库存不足等情况,我国在应用该方式上仍具有局限性,因此,化疗仍是多数患者的主要治疗方式。地西他滨是种 DNA 甲基转移酶抑制剂,可对 DNA 去甲基化及造血细胞分化产生诱导作用,目前该药物已被批准应用到中、高危髓增生异常综合征的治疗中^[2,3]。随着医学技术的不断发展,中医药联合化疗的方案也已普遍应用,其中参芪扶正注射液具有增加机体免疫力、提高化疗疗效的作用,并有助于促进造血^[4]。已有较多研究显示肝细胞生长因子(HGF)、血管内皮生长因子(VEGF)与乳酸脱氢酶(LDH)的水平和血液系统肿瘤的发生、发展之间也存着的紧密的联系,有助于评价病情变化^[5,6]。因此,应用参芪扶正注射液联合地西他滨的治疗本研究旨在探讨在急性髓系白血病患者中优势,并探讨其对血清 HGF、VEGF 及 LDH 水平的影响,现报道如下。

1 资料与方法

1.1 一般资料

选择 2014 年 8 月至 2016 年 8 月我院接诊的 84 例急性髓系白血病患者。纳入标准^[7]:①符合急性髓系白血病诊断标准,并通过血常规、骨髓检查、组织化学染色等得以确诊;②年龄 18~60 岁;③知情同意此次研究。排除标准^[8]:①无法耐受化疗;②对研究药物过敏;③肝、肾功能障碍;④伴有糖尿病、脑部疾病、恶性肿瘤、自身免疫性疾病等。以随机数表法分为 2 组,各 42 例。观察组男 23 例,女 19 例;年龄 21~57 岁,平均(39.78±4.59)岁;其中 M₁ 型 7 例,M₂ 型 20 例,M₃ 型 4 例,M₄ 型 4 例,M₅ 型 5 例,M₆ 型 2 例。对照组男 25 例,女 17 例;年龄 23~58 岁,平均(40.12±4.48)岁;M₁ 型 6 例,M₂ 型 19 例,M₃ 型 5 例,M₄ 型 5 例,M₅ 型 6 例,M₆ 型 1 例。两组一般资料比较差异无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

对照组进行地西他滨+DA 化疗方案,第 1~5d,地西他滨(规格 50 mg,厂家:江苏豪森药业股份有限公司,国药准字 H20130067)15 mg/(m²·d);第 3~6d;柔红霉素(规格 20 mg,厂

家:浙江海正药业股份有限公司,国药准字 H33020925),剂量 40~60 mg/(m²·d);第 3~9d,阿糖胞苷(规格 100 mg,厂家:Hospira Australia Pty Ltd.,国药准字 H20120187),剂量 100 mg/(m²·d)。

观察组联合参芪扶正注射液(规格 250 mL/瓶,厂家:丽珠集团利民制药厂,国药准字 Z19990065),剂量 250 mL 静脉滴注,1 次/d;联用 9d,和对照组化疗同步。

两组均以 21d 为 1 个周期,连续治疗 2 个周期。

1.3 观察指标

1.3.1 血常规 包括白细胞计数(WBC)、血红蛋白(HGB)、血小板计数(PLT)、中性粒细胞计数(NEU);

1.3.2 血清因子 抽取 3 mL 空腹静脉血,肝细胞生长因子(HGF)、血管内皮生长因子(VEGF)、乳酸脱氢酶(LDH),以 OLYMPUS AU2700 全自动生化分析仪检测,均采用酶联免疫吸附法,试剂盒购于上海基免实业有限公司;

1.3.3 不良反应。

1.4 疗效评定标准

参照《血液病诊断及疗效标准》^[9],完全缓解(CR):临床症状得到消失,HGB≥90 g/L(女),或 HGB≥100 g/L,NEU≥1.5×10⁹/L,PLT≥100×10⁹/L,通过细胞学检查结果显示不存在白血病细胞,骨髓检查结果显示幼稚淋巴细胞、原始淋巴细胞计数≤5%;部分缓解(PR):临床症状有所缓解,血常规检查结果其中一项未达到 CR 标准,或骨髓检查结果显示幼稚淋巴细胞、原始淋巴细胞计数 6%~20%;无缓解(NR):临床症状、血常规、骨髓检查结果均未达到 CR、PR 标准。以 CR+PR 为总缓解率。

1.4 统计学分析

以 spss18.0 软件包处理,计量资料用均数±标准差($\bar{x} \pm s$)表示,组间比较采用 t 检验,计数资料组间比较采用 χ^2 检验,以 P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组治疗前后血常规的比较

治疗前,两组血常规指标比较差无显著异(P>0.05);治疗后,两组 WBC、HGB、PLT、NEU 较治疗前均显著改善(P<0.05),且观察组 WBC 明显低于对照组,HGB、PLT、NEU 明显高于对照组(P<0.05),见表 1。

表 1 两组治疗前后血常规比较($\bar{x} \pm s$)

Table 1 Comparison of the routine blood test between two groups before and after treatment($\bar{x} \pm s$)

Groups		WBC(× 10 ⁹ /L)	HGB(g/L)	PLT(× 10 ⁹ /L)	NEU(× 10 ⁹ /L)
Observation group(n=42)	Before treatment	8.72± 1.34	61.28± 4.59	66.23± 4.64	0.48± 0.12
	After treatment	4.10± 0.69**	88.73± 6.24**	89.04± 6.32**	1.32± 0.24**
Control group(n=42)	Before treatment	8.79± 1.30	61.35± 4.55	66.15± 4.69	0.51± 0.10
	After treatment	5.92± 0.83*	73.40± 5.07*	75.89± 5.20*	0.96± 0.21*

Note: Vs the before treatment, *P<0.05; vs the control group, **P<0.05.

2.2 两组治疗前后血清 HGF、VEGF 与 LDH 水平的比较

治疗前,两组血清 HGF、VEGF 与 LDH 水平比较差异无统计学意义(P>0.05);治疗后,两组血清 HGF、VEGF 与 LDH 水平比较较治疗前均显著降低(P<0.05),观察组血清 HGF、

VEGF 与 LDH 比较均明显低于对照组(P<0.05),见表 2。

2.3 两组临床疗效的比较

观察组总缓解率为 95.23%,明显高于对照组(73.81%,P<0.05),见表 3。

表 2 两组治疗前后血清 HGF、VEGF 与 LDH 水平的比较($\bar{x} \pm s$)Table 2 Comparison of the routine blood test results between two groups ($\bar{x} \pm s$)

Groups		HGF(pg/mL)	VEGF(pg/mL)	LDH(U/L)
Observation group(n=42)	Before treatment	984.58± 137.45	95.74± 13.40	637.45± 42.37
	After treatment	479.56± 85.03* [#]	56.25± 8.23* [#]	288.96± 25.62* [#]
Control group(n=42)	Before treatment	990.08± 131.23	96.12± 13.05	635.39± 43.15
	After treatment	678.34± 92.43*	70.43± 10.37*	402.72± 29.45*

Note: Vs the before treatment, *P<0.05; vs the control group, [#]P<0.05.

表 3 两组临床疗效比较(例, %)

Table 3 Comparison of the clinical efficacy between two groups (n, %)

Groups	CR	PR	NR	Total remission rate
Observation group(n=42)	28(66.67)	12(28.57)	2(4.76)	40(95.23)*
Control group(n=42)	15(35.71)	16(38.09)	11(26.19)	31(73.81)

Note: Vs the control group, *P<0.05.

2.4 两组不良反应发生情况的比较

显低于对照组 (P<0.05), 见表 4。

观察组恶心呕吐、感染、多汗、出血、心脏毒性发生率均明

表 4 两组不良反应的发生情况比较(例, %)

Table 4 Comparison of the incidence of adverse reaction between two groups (n, %)

Groups	Nausea and vomiting	Infected	Hyperhidrosis	Hemorrhage	Cardiotoxicity
Observation group(n=42)	11(26.19)*	4(9.52)*	5(11.90)*	5(11.90)*	1(2.38)*
Control group(n=42)	23(54.76)	15(35.71)	14(33.33)	15(35.71)	7(16.67)

Note: compared with the control group, *P<0.05.

3 讨论

急性髓系白血病临床症状主要表现为出血、贫血、发热、器官浸润等,在治疗中预后较差。在此类患者治疗中,首选 DA 化疗方案。近年来,较多学者认为 DNA 甲基化在骨髓增生异常综合征转变为急性髓系白血病过程中起着重要作用,而去甲基化治疗可作为该病的新治疗靶点^[10,11]。地西他滨作为去甲基化药物,抑制甲基化转移酶作用明显,可令 DNA 甲基化过程得以逆转,但化疗药物在杀伤白血病细胞同时,在一定程度上会对正常造血、免疫功能等造成影响,增加感染、贫血、出血等不良反应,影响预后^[12]。

中医认为急性髓系白血病属虚癆、正虚、血证,和正气不足、毒素内生密切相关,在治疗过程中,补血益气、扶正固本,在促进骨髓造血、机体免疫力及缓解化疗毒副反应中具有积极意义。参芪扶正注射液主要成分为党参、黄芪。国内外均有报道证实党参中富含人参皂苷,可产生养血生津、补中益气、健脾胃等功效,有助于提高免疫力,减轻化疗所造成的损伤,并可抑制肿瘤细胞生长,缓解缺血再灌注损伤;黄芪中包含黄酮类、黄芪多糖、皂苷类等多种有效成分,具有除烦渴、补中益气之效,可促进骨髓造血,改善机体免疫力^[13,14]。

本研究结果显示联合参芪扶正注射液的患者 WBC、HGB、PLT、NEU 的改善程度明显优于地西他滨治疗的患者,且临床疗效总缓解率高达 95.23%, 明显比使用地西他滨患者的 73.81%高。Wang LX 等^[15]报道称参芪扶正注射液在促进骨髓造血功能效果令人满意。Wang L 等^[16]研究也指出参芪扶正注射液和化疗药物联用可缓解化疗毒性,提高临床疗效。以上研究

均和本研究具有相似性。此外,联合参芪扶正注射液的患者恶心呕吐、感染、多汗、出血、心脏毒性发生率分别为 26.19%、9.52%、11.90%、11.90%、2.38%, 明显较参芪扶正注射液降低。Ai QH 等^[17]分析中提出参芪扶正注射液可对患者体内对 T 细胞的分泌进行调节,降低叉头蛋白 P3 的表达,对 Treg 功能具有抑制作用,令 Treg 对机体免疫抑制作用减轻,提高免疫力,继而缓解毒副反应。因此,我们认为采用合理有效的化疗方案并联合参芪扶正注射液,可促进骨髓造血,改善 WBC、HGB、PLT、NEU 的表达,提高疾病缓解率,且有助于减少不良反应。

国内外均有研究显示在急性髓系白血病患者中,不仅存在骨髓中造血干/祖细胞的发育、分化障碍外,和骨髓造血微环境中的基质细胞功能障碍也存在着密切的关系^[18,19]。HGF 在人体免疫网络中起着重要作用,若其表达异常,可反映出骨髓造血微环境的改变。Reikvam H 等^[20]等研究中显示在白血病细胞中,可有 HGF 的分泌,且在骨髓、血液中均有高表达的 HGF,其在急性髓系白血病的发生、发展、侵袭过程中发挥着重要作用。VEGF 在血管形成中是一种重要刺激因子,已有较多研究证实急性髓系白血病、慢性淋巴细胞白血病、急性淋巴细胞白血病等患者中均有 VEGF 及其受体表达,高表达的 VEGF 会对血管内皮细胞造成刺激,且可通过自分泌、旁分泌的方式,刺激白血病细胞增值^[21,22]。而在急性髓系白血病患者中,由于肿瘤细胞转移、侵袭等,会致使周围组织出血缺氧、缺血等,增加细胞通透性,令正常的有氧代谢酶转化为无氧酵解,而无氧酵解会诱导细胞释放高浓度的 LDH^[23]。Park S 等^[24]报道中显示,在急性髓系白血病患者中 LDH 的表达明显高于正常人,且和疾病严重程度呈正相关。因此,对血清 HGF、VEGF、LDH 的检测,有助

于进一步判断疾病变化。本研究结果显示,联合参芪扶正注射液的患者血清 HGF、VEGF、LDH 降低程度明显优于地西他滨治疗的患者,分析原因可能和参芪扶正注射液可增加气血吸收、脾胃运化,令气血旺盛、血脉充盈,令药物代谢速度、血管内皮通透性增加,并具有增加机体免疫力等作用相关^[25,26],但具体作用机制仍需进一步深入研究。

综上所述,参芪扶正注射液联合地西他滨治疗急性髓系白血病患者效果显著,有助于提高临床疗效,降低毒副反应,其内在机制可能和降低血清 HGF、VEGF、LDH 的水平相关。

参考文献(References)

- [1] Duarte FB, Lemes RPG, Dos Santos TEJ, et al. Presence of new mutations in the TP53 gene in patients with low-risk myelodysplastic syndrome: two case reports[J]. J Med Case Rep, 2017, 11(1): 143
- [2] Zhao H, Xu L, Yang Y, et al. Successful Management of Decitabine prior to Full-Dose Idarubicin and Cytarabine in the Treatment of Refractory/Recurrent Acute Myeloid Leukemia [J]. Acta Haematol, 2017, 137(4): 195-200
- [3] Raneros AB, Puras AM, Rodriguez RM, et al. Increasing TIMP3 expression by hypomethylating agents diminishes soluble MICA, MICB and ULBP2 shedding in acute myeloid leukemia, facilitating NK cell-mediated immune recognition [J]. Oncotarget, 2017, 8(19): 31959-31976
- [4] Dong BY, Wang C, Tan L, et al. Inhibitory effect of Shenqi Fuzheng injection combined with docetaxel on lung cancer cells[J]. J Zhejiang Univ Sci B, 2017, 18(1): 76-78
- [5] Machado-Neto JA, de Melo Campos P, Olalla Saad ST, et al. YAP1 expression in myelodysplastic syndromes and acute leukemias [J]. Leuk Lymphoma, 2014, 55(10): 2413-2415
- [6] Yang XW, Ma LM, Zhao XQ, et al. Clinical Curative Efficacy of Lenalidomide Combined with Chemotherapy for Acute Leukemia and Its Impact on VEGF [J]. Chinese Journal of Experimental Hematology, 2016, 24(3): 702-706
- [7] Ross DW, Wanchoo R, Guigova A, et al. Light chain Fanconi syndrome in a patient with acute myeloid leukemia and monoclonal gammopathy of undetermined significance [J]. CEN Case Rep, 2016, 5(2): 238-241
- [8] Nakamura Y, Matsuguma M, Tokunaga Y, et al. Successful Treatment of Behçet's Disease Associated with Acute Myeloid Leukemia with Myelodysplasia-related Changes Using Azacitidine and Tacrolimus before Allogeneic Hematopoietic Stem Cell Transplantation[J]. Intern Med, 2017, 56(10): 1199-1202
- [9] Zahedipour F, Ranjbaran R, Behzad Behbahani A, et al. Development of Flow Cytometry-Fluorescent In Situ Hybridization (Flow-FISH) Method for Detection of PML/RARα Chromosomal Translocation in Acute Promyelocytic Leukemia Cell Line [J]. Avicenna J Med Biotechnol, 2017, 9(2): 104-108
- [10] Kobayashi Y. Current diagnosis and treatment for acute myeloid leukemia[J]. Rinsho Ketsueki, 2017, 58(4): 364-372
- [11] Liu XL, Zhao X, Wang C, et al. Decitabine treatment for acute myeloid leukemia relapse after allogeneic hematopoietic stem cell transplantation [J]. J Biol Regul Homeost Agents, 2017, 31(1): 171-175
- [12] Gerds AT, Mukherjee S. A New Style of Transplantation May Gain Points When Treating Older Patients with Acute Myeloid Leukemia [J]. Biol Blood Marrow Transplant, 2017, 23(5): 715-716
- [13] Cai YM, Zhang Y, Zhang PB, et al. Neuroprotective effect of Shenqi Fuzheng injection pretreatment in aged rats with cerebral ischemia/reperfusion injury[J]. Neural Regen Res, 2016, 11(1): 94-100
- [14] Mori M, Tottone L, Quaglio D, et al. Identification of a novel chalcone derivative that inhibits Notch signaling in T-cell acute lymphoblastic leukemia[J]. Sci Rep, 2017, 7(1): 2213
- [15] Wang LX, Xie YM, Ai QH, et al. Clinical safety studies based on 30 026 post-marketing cases of Shenqi Fuzheng injection by intensive hospital monitoring nested NCCS [J]. Chinese Journal of traditional Chinese Medicine, 2015, 40(24): 4739-4745
- [16] Wang L, Qu H. Development and optimization of SPE-HPLC-UV/ELSD for simultaneous determination of nine bioactive components in Shenqi Fuzheng Injection based on Quality by Design principles[J]. Anal Bioanal Chem, 2016, 408(8): 2133-2145
- [17] Ai QH, Zeng XB, Xie YM, et al. Analysis suspected allergic factors to shenqi fuzheng injection based on prescription sequence analysis and nested case control study [J]. Chinese Journal of traditional Chinese Medicine, 2014, 39(18): 3563-3566
- [18] Safari S, Movafagh A, Zare-Adollahi D, et al. MST1/2 and YAP1 gene expression in acute myeloid leukemia [J]. Leuk Lymphoma, 2014, 55(9): 2189-2191
- [19] Dalamaga M, Karmaniolas K, Chamberland J, et al. Higher fetuin-A, lower adiponectin and free leptin levels mediate effects of excess body weight on insulin resistance and risk for myelodysplastic syndrome[J]. Metabolism, 2013, 62(12): 1830-1839
- [20] Reikvam H, Hatfield KJ, Fredly H, et al. The angioregulatory cytokine network in human acute myeloid leukemia - from leukemogenesis via remission induction to stem cell transplantation [J]. Eur Cytokine Netw, 2012, 23(4): 140-153
- [21] Nie DM, Wu QL, Zhu XX, et al. Angiogenic factors are associated with development of acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation [J]. J Huazhong Univ Sci Technol Med Sci, 2015, 35(5): 694-699
- [22] Reikvam H, Brenner AK, Hagen KM, et al. The cytokine-mediated crosstalk between primary human acute myeloid cells and mesenchymal stem cells alters the local cytokine network and the global gene expression profile of the mesenchymal cells[J]. Stem Cell Res, 2015, 15(3): 530-541
- [23] Hiller JK, Schmoor C, Gaidzik VI, et al. Evaluating the impact of genetic and epigenetic aberrations on survival and response in acute myeloid leukemia patients receiving epigenetic therapy [J]. Ann Hematol, 2017, 96(4): 559-565
- [24] Park S, Huh HJ, Mun YC, et al. Calreticulin mRNA expression and clinicopathological characteristics in acute myeloid leukemia [J]. Cancer Genet, 2015, 208(12): 630-635
- [25] Zhang SY, Fan CL, Huang XJ, et al. A new phenylpropanoid and a new isoflavone glycoside from Shenqi Fuzheng Injection [J]. J Asian Nat Prod Res, 2015, 17(3): 274-279
- [26] Li J, Wang JC, Ma B, et al. Shenqi Fuzheng Injection for advanced gastric cancer: a systematic review of randomized controlled trials[J]. Chin J Integr Med, 2015, 21(1): 71-79