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贞芪扶正颗粒对去甲氧柔红霉素联合阿糖胞苷方案治疗成人急性髓系白血病疗效及毒副反应的影响*

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摘要 目的:研究贞芪扶正颗粒对去甲氧柔红霉素联合阿糖胞苷方案治疗成人急性髓系白血病疗效及毒副反应的影响。**方法:**选取我院 2006 年 2 月 ~2012 年 8 月期间收治的成人急性髓系白血病患者 134 例,并将其随机分为对照组与观察组。对照组采用去甲氧柔红霉素 + 阿糖胞苷方案规范诱导缓解治疗,观察组在对照组治疗方案上加用贞芪扶正颗粒,观察和比较两组的临床疗效及不良反应的发生情况。**结果:**对照组与观察组的完全缓解率(CR)分别为 73.2%(41/56)和 79.5%(62/78),中位 OS 分别为 13.9 个月和 14.6 个月,两组比较差异均无统计学意义(P>0.05)。观察组 III 级以上的骨髓抑制现象的发生率显著低于对照组(P<0.05),粒细胞最低值显著高于对照组(P<0.05),粒细胞缺乏和血小板降低持续的总体时间均明显短于对照组(P<0.05);观察组各主要感染部位的发生率及感染总体发生率均显著低于对照组(P<0.05);观察组各种主要非血液学毒副反应包括呕吐、腹泻、肝毒性、肾毒性、神经毒性、心率失调、口腔炎症、皮疹及发热等的发生率显著低于对照组(73.1% vs. 100%,P<0.05)。**结论:**贞芪扶正颗粒能够有效改善去甲柔红霉素联合阿糖胞苷方案治疗成人急性髓系白血病的毒副反应,且不影响其临床疗效。

关键词:贞芪扶正颗粒;去甲氧柔红霉素;阿糖胞苷;急性髓系白血病;毒副反应

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Effect of Zhenqifuzheng Granules on the Clinical Efficacy and Toxicity Reaction of Idarubicin and Cytarabine in the Treatment of Adult Acute Myeloid Leukemia*

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ABSTRACT Objective: To investigate the effect of Zhenqifuzheng granules on the clinical efficacy and adverse reactions of idarubicin and cytarabine in the treatment of adult acute myeloid leukemia. **Methods:** 134 cases of patients with acute myeloid leukemia admitted in our hospital from Febuary 2006 to August 2012 were randomly divided into the control group and observation group. The patients in control group were given idarubicin and cytarabine in order to reach remission, while the patients in observation were treated by the therapeutic schedule with zhenqi fuzheng granule. The clinical effect and incidence of adverse effects of patients were observed and compared between two groups. **Results:** The complete remission(CR) rate of control group and observation group were 73.2%(41/56) and 79.5%(62/78) respectively(P>0.05), the median overall survival(OS) were 13.9 and 14.6 months respectively(P>0.05). The incidence rates of grade III and higher grade bone marrow suppression, infection were all significantly lower in the observation group than those of the control group (P<0.05), the minimum of granulocyte was obviously higher than that of the control group (P<0.05), the duration of agranulocytosis and thrombocytopenia were both shorter in observation group (P<0.05). The incidence rate of non-hematology side effects such as vomiting, diarrhea, hepatotoxicity, nephrotoxicity, neurotoxicity, disorder of heart rates, rash, pyrexia and so on was significantly lower than that of the control group(73.1% vs. 100%, P<0.05). **Conclusion:** Zhenqi fuzheng granule could effectively reduce the side effect of idarubicin and cytarabine in the treatment of adult acute myeloid leukemia, but had little effect on the clinical efficacy.

Key words: Zhenqifuzheng granules; Idarubicin; Cytarabine; Acute myeloid leukemia; Adverse effect

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前言

急性髓系白血病(acute myeloid leukemia,AML)是恶性程度极高的一类血液系统肿瘤,成人所罹患的白血病中约有 80%为 AML,20%为急性淋巴细胞白血病 (acute lymphoblastic leukemia,ALL)[1,2]。目前,治疗 AML 的主要方案是以蒽环 / 蒽醌类抗生素联合阿糖胞苷为基础的标准诱导缓解化疗方案,近年研究发现去甲氧柔红霉素 + 阿糖胞苷(Idarubicin+Cytarabine,IA)治疗 AML 的疗效优于其他蒽环类药物,其有效完全缓解率可达 60%-80%[3,4],目前已广泛运用于 AML 的临床治疗中,但伴随而来的多种毒副反应严重损害了患者的治疗效果及方案依从性[5-7]。因此,进一步探究及改善 IA 方案的疗效及降低毒副反应的发生率对于提高 AML 患者的临床预后具有重要意义。本研究旨在观察贞芪扶正颗粒(吉林敖东药业)对去甲氧柔红霉素(艾诺宁,浙江海正药业)联合阿糖胞苷(注射用盐酸阿糖胞苷,哈尔滨莱博通药业)方案治疗成人急性髓系白血病的临床疗效及毒副作用的影响,现将结果报道如下。

1 资料与方法

1.1 一般资料

依据《血液病诊断及疗效标准》对于 2006 年 2 月至 2012 年 8 月在我院血液科收治住院的 146 例成人急性白血病患者通过外周血象、骨髓细胞学涂片、免疫活检及免疫标记等检查项目予以明确诊断,其共有 134 例符合成人急性髓系白血病诊断。采用随机分组的方式,将 134 名患者分为对照组及观察组,详细临床资料见表 1。两组患者在治疗前均无严重的脏器功能受损或衰竭,且无严重全身感染等并发症。一般资料组间差异比较均无统计学意义(P>0.05),具有可比性,见表 1。

表 1 两组患者一般临床特征的比较

Table 1 The comparison of clinical feature between two groups

	Control Group	Observation Group
N	56	78
Sex		
Man	22(39.3%)	32(41.0%)
Woman	34(60.7%)	46(59.0%)
Medium Age	39(13~69)	41(14~75)
AML Type		
M1/M2	5/14	8/24
M4/M5	4/26	2/37
M6/M7	2/0	3/0
Undifferentiated Type	5	4
Medium WBC(× 10^9/L)	20.3(0.6~174.4)	18.1(0.73~226.7)
Medium HB(g/L)	73(18~144)	78(21~132)
Medium PLT(× 10^9/L)	68.4(16~563)	54.2(9~333)

1.2 治疗方案

对照组采用 IA 方案进行诱导缓解治疗:去甲氧柔红霉素(IDA)8-10 mg/(m^2·d),静脉滴注,每日 1 次,共 3 日;阿糖胞苷(Ara-C)100-200 mg/(m^2·d)静脉滴注,每日 1 次,共 7 日。观察组则在对照组化疗方案基础上加用贞芪扶正颗粒加以治疗,1 次 1 袋,口服,每日 2 次,持续服用 30 日。两组均应用方案治疗 1~2 个疗程的诱导缓解治疗后判断疗效。两组患者方案实施前若白细胞总数≥ 50× 10^9/L,则应先口服羟基脲 3 g/d,以减轻患者白细胞负荷,并预防肿瘤溶解综合征。化疗前后及化疗期间定期对受试患者行血常规复查(每 3~4 日),肝肾功能复查(每 4~5 日),心肌酶谱及心电图检测,记录患者中性粒细胞缺乏发生时间及持续时间(以低于 0.5× 10^9/L 为标准),血小板及血红蛋白降低持续时间等。每日监测患者体温变化情况,注意有无严重感染发生以及其他系统发生的不良反应。本研究病例随访至 2013 年 12 月 31 日。

1.3 支持治疗

两组方案实施期间均给于营养支持护理、保肝、止吐等对症常规支持治疗。治疗期间防治感染,患者如若出现粒细胞重度减少,则采用 G-CSF 或 GM-CSF 予以应急治疗;重度贫血者给予输血或成分输血等支持治疗。发生严重感染则依据症状及病原学、影像学等辅助诊断选择恰当抗生素予以抗感染治疗。

1.4 统计学分析

采用 SPSS14.0 软件对所收集的数据进行统计学分析。计量资料以均数± 标准差($\bar{x}$± s)表示,组内治疗前后的情况比较作配对 t 检验;计数资料则以百分率表示,两组比较采用卡方检验,以 P<0.05 为差异有统计学意义的标准。

2 结果

2.1 两组临床疗效的比较

对照组和观察组依照治疗方案完成后总有效率分别为 78.6%(44/56) 和 89.7%(70/78), 组间比较差异无统计学意义(P>0.05); 两组完全缓解率 (completely remission,CR) 分别为 73.2%(41/56)和 79.5%(62/78),差异亦无统计学意义(P>0.05),详见表 2。

表 2 两组临床疗效的比较

Table 2 Comparison of the clinical efficacy between two groups

	CR(%)	PR(%)	NR(%)	CR+PR(%)
Control group	41/56(73.2%)	3/56(5.4%)	12/56(21.4%)	44/56(78.6%)
Observation group	62/78(79.5%)	8/78(10.3%)	8/78(10.3%)	70/78(89.7%)
P value	>0.05			>0.05

2.2 两组临床预后情况的比较

Kaplan-meier 生存分析结果显示两组患者的中位生存期分别为 13.9 个月(1.5~77.3 个月)与 14.6 个月(0.8~73.2)个月,差异无统计学意义(P>0.05),见图 1。

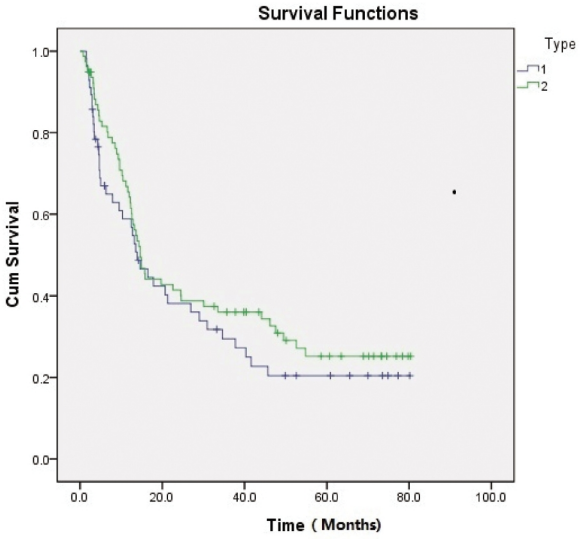

图 1 两组临床预后情况的比较

Fig. 1 Comparison of the clinical prognosis between two groups

2.3 两组毒副反应发生情况的比较

2.3.1 两组血液学毒性发生情况的比较 两组患者均发生了III级以上的骨髓抑制现象，且观察组的发生率显著低于对照组(P<0.05)。观察组患者粒细胞最低值显著高于对照组(P=0.027)，粒细胞缺乏持续的总体时间优于对照组(P=0.046)。两组患者血小板最低值比较差异无统计学意义(P=0.355)，但观察组血小板降低的持续时间明显短于对照组(P=0.042)，见表 3。

2.3.2 两组感染发生情况的比较 两组患者在分别依照方案进行化疗时，均发生了不同程度的感染(见表 4)。感染主要见于肺及呼吸道、口腔黏膜、肠道、皮肤、血液与其他部位，观察组各主要感染部位的发生率及感染总体发生率均显著低于对照组(100% vs. 60.3%，P<0.05)。

2.3.3 两组非血液学毒副反应发生情况的比较 两组患者主要非血液学毒副反应包括呕吐、腹泻、肝毒性、肾毒性、神经毒性、心率失调、口腔炎症、皮疹及发热等，观察组各种非血液学毒副反应的发生率显著低于对照组 (73.1% vs. 100%，P<0.05)(见表 5)。

表 3 两组血液学毒性发生情况的比较

Table 3 The comparison of incidence of hematological toxicity between two groups

	Minimum of granulocyte ($\times 10^9$)	Duration of agranulocytosis (d)	Minimum of plates ($\times 10^9$)	Duration of thrombocytopenia (d)
Control group	0.04± 0.12	28.5± 5.4	35.66± 9.78	17.2± 6.9
Observation group	0.33± 0.09	11.9± 4.6	42.14± 7.46	9.8± 3.7
P value	0.027	0.046	0.355	0.042

表 4 两组感染发生情况的比较

Table 4 The comparison ofincidence of infection between two groups

	Control group	Observation group
Lung infection	18/56(32.1%)	14/78(17.9%)
Oral infection	14/56(25.0%)	10/78(12.8%)
Intestinal infection	11/56(19.6%)	13/78(16.7%)
Skin infection	9/56(16.1%)	5/78(6.4%)
Blood infection	8/56(14.3%)	4/78(5.1%)
Others	4/56(7.1%)	1/78(1.3%)
Overall	64/56(100%)	47/78(60.3%)
P value		<0.05

表 5 两组非血液学毒副反应发生情况的比较

Table 5 The comparison ofincidence of non- hematological toxicity between two groups

	Control group(%)	Observation group(%)
Vomiting	17/56(30.3%)	13/78(16.7%)
Diarrhea	9/56(16.1%)	4/78(5.1%)
Hepatotoxicity	13/56(23.2%)	11/78(14.1%)
Nephrotoxicity	2/56(3.6%)	2/78(2.6%)
Neurotoxicity	2/56(3.6%)	0/78(0)
Disorder of heart rates	10/56(17.9%)	10/78(12.8%)
Stomatitis	11/56(19.6%)	10/78(12.8%)
Rash	6/56(10.7%)	4/78(5.1%)
Pyrexia	5/56(8.9%)	3/78(3.8%)
Overall	75/56(100%)	57/78(73.1%)
P value		<0.05

3 讨论

急性髓系白血病是造血干 / 祖细胞的恶性克隆性疾病，白血病细胞分化停止在早期阶段，以原始细胞和早期幼稚细胞为主。这些大量异常增殖的细胞阻滞了骨髓中正常造血细胞的分化。目前，治疗方案的主要思路为通过 1~2 疗程的诱导缓解化疗使患者能够快速有效完全缓解，此后再加以缓解后剂量递增、时间密集的化疗，以期清除白血病微小残留病变[8]。近年来研究发现以去甲氧柔红霉素替代经典诱导缓解方案中的柔红霉素可有效提高急性髓系白血病患者的临床缓解率并延长其生存期[9-11]，这是由于去甲氧柔红霉素较柔红霉素具有更高的脂溶性，易于透过细胞膜，且能够更有效的诱导 DNA 链断裂，抑制 DNA 和 RNA 多聚酶；其体内转化产物醇式去甲氧柔红霉素半衰期长，可在体内持续发挥作用，其抗肿瘤活性是柔红霉素的 4~8 倍。但以骨髓抑制为代表的众多化疗毒副反应并未随去甲氧柔红霉素的出现而有所改观，与柔红霉素 + 阿糖胞苷相比，去甲氧柔红霉素 + 阿糖胞苷的化疗方案无论是血液学毒副反应或是非血液学毒副反应，均具有相似的发生率，这极大的影响了疗效及患者对治疗的依从性[12,13]。因此，探寻改善化疗方案毒副反应的手段对进一步提高方案疗效具有重要的临床现实意义。

我国传统医学中补血活血类药物具有效果显著、经济低廉、少有不良反应等特点，目前已逐渐引起人们的广泛关注。贞

芪扶正颗粒为纯中药复方制剂,其主要成分为黄芪、女贞子,具有“扶正培本”、“扶正祛邪”等之功效[14,15],可提高人体免疫机能,保护骨髓及肾上腺皮质功能,适用于各种疾病引起的虚损;配合手术、放疗、化疗等具有较好的辅助治疗作用,可显著提高患者的远期疗效[16-18]。苗明三等[19]在环磷酰胺所致的小鼠血虚模型的研究中发现,贞芪扶正颗粒可有效改善外周血血细胞状况及骨髓象,保护骨髓造血功能和促进造血细胞增殖的功效。这也提示贞芪扶正颗粒对于化疗期间所导致的骨髓抑制等血液学毒副反应具有一定的预防及治疗作用。

本研究旨在观察贞芪扶正颗粒对去甲氧柔红霉素+阿糖胞苷治疗 AML 的临床疗效以及毒副反应的影响。实验结果提示加用贞芪扶正颗粒组与单用去甲氧柔红霉素+阿糖胞苷组治疗 AML 的疗效相近,不劣于单独化疗。而加用贞芪扶正颗粒可有效改善 AML 患者粒细胞缺乏的状况,缩短粒细胞缺乏及血小板降低的持续时间,显著减少患者 III 级以上骨髓抑制事件的发生率。比较两组并发感染情况的发生时,研究发现贞芪扶正颗粒可明显降低去甲氧柔红霉素联合阿糖胞苷而治疗所致的感染的发生率(100% vs. 60.3%, P<0.05),这也提示该药具有强化机体免疫功能的功效。此外,贞芪扶正颗粒辅助治疗还可以显著降低 AML 患者非血液学毒副反应的发生率也(100% vs. 73.1%, P<0.05)。以上结果均提示在应用去甲氧柔红霉素+阿糖胞苷治疗急性髓系白血病时,联合贞芪扶正颗粒不影响 AML 患者的整体疗效,并且能够有效降低该方案所致的多种毒副反应的发生率,提高患者的机体免疫机能,减少因不良反应而导致的治疗方案终止。

目前,急性髓系白血病仍是成人常见高发的血液系统恶性肿瘤,严重威胁患者的生命健康。关于其治疗的研究中虽已取得巨大进步,但距离维持患者长期生存乃至治愈仍任重道远。贞芪扶正颗粒辅助治疗能够减少去甲氧柔红霉素联合阿糖胞苷治疗的 AML 患者的毒副反应发生,且并不降低化疗疗效,可有效保护患者的造血系统功能和提高患者的免疫机能。由此可见,传统医学关于补血活血的理念具有一定的临床实践意义[20],我们在此后的研究中将继续深入挖掘中药中成药在改善血液肿瘤化疗的应用价值,为其临床治疗提供进一步的研究证据。

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