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甲氨蝶呤治疗急性淋巴细胞白血病的疗效及对患者 BAFF、APRIL 的影响 *

王 瑾 刘海玲 姚 欢 张王刚 马肖容△

（西安交通大学第二附属医院血液内科 陕西 西安 710000）

摘要 目的：探讨甲氨蝶呤治疗急性淋巴细胞白血病的疗效及对患者 B 淋巴细胞刺激因子（BAFF）、增殖诱导配体（APRIL）的影响。**方法：** 选择 2016 年 8 月至 2018 年 9 月我院收治的急性淋巴细胞白血病患者 50 例进行研究，以随机数表法分为观察组（n=26）和对照组（n=24）。对照组给予化疗治疗，观察组采用甲氨蝶呤治疗。比较两组患者的临床疗效、BAFF、APRIL、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 水平变化情况及不良反应发生情况。**结果：**治疗后，观察组总有效率 84.62%显著高于对照 58.33%，差异显著（$P<0.05$）；治疗前，两组 BAFF、APRIL 水平无显著差异（$P>0.05$）；治疗后，两组 BAFF、APRIL 水平均显著下降，且观察组低于对照组（$P<0.05$）；治疗前，两组 T 淋巴细胞亚群水平无显著差异（$P>0.05$）；治疗后，两组 T 淋巴细胞亚群水平均显著改善，且观察组 $CD4^+$、$CD4^+/CD8^+$ 高于对照组，$CD8^+$ 低于对照组（$P<0.05$）；两组患者不良反应发生情况均无统计学意义（$P>0.05$）。**结论：**在急性淋巴细胞白血病患者中应用甲氨蝶呤效果显著，可有效改善患者 BAFF、APRIL 水平。

关键词：甲氨蝶呤；急性淋巴细胞白血病；B 淋巴细胞刺激因子；增殖诱导配体

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Curative efficacy of methotrexate in treatment of Acute Lymphocytic Leukemia and Its Effectson Patients' BAFF and APRIL*

WANG Jin, LIU Hai-ling, YAO Huan, ZHANG Wang-gang, MA Xiao-rong△

（The Second Affiliated Hospital of Xi'an Jiaotong University, Department of Hematology, Xi'an, Shaanxi, 710000, China）

ABSTRACT Objective: To study Curative efficacy of methotrexate in treatment of Acute lymphocytic leukemiaand its effectson patients' B lymphocyte stimulating factor (BAFF), proliferation-induced ligand (APRIL). **Methods:** 50 patients with acute lymphoblastic leukemia admitted to our hospital from August 2016 to September 2018 were selected for the study, were divided into observation group (n=52) and control group (n=48) by random number table method. The control group was treated with chemotherapy and the observation group was treated with methotrexate on the basis of the control group. The clinical efficacy, BAFF, APRIL, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ levels and adverse reactions of patients in the two groups were compared. **Results:** After treatment, the total effective rate of 84.62% in the observation group was significantly higher than that in the control group 58.33%, with a significant difference ($P < 0.05$). Before treatment, there was no significant difference in BAFF and APRIL levels between the two groups ($P>0.05$). After treatment, BAFF and APRIL levels in both groups decreased significantly, and the observation group was lower than the control group ($P<0.05$). Before treatment, there was no significant difference in T lymphocyte subsets between the two groups ($P>0.05$). After treatment, T lymphocyte subsets in both groups were significantly improved, and $CD4^+$, $CD4^+/CD8^+$ in the observation group were higher than those in the control group, while $CD8^+$ was lower than those in the control group ($P<0.05$). The incidence of adverse reactions in the two groups was not statistically significant ($P>0.05$). **Conclusion:** Methotrexate has a significant effect in patients with acute lymphoblastic leukemia, and can effectively improve the BAFF and APRIL levels of patients.

Key words: Methotrexate; Acute lymphocytic leukemia; B lymphocyte stimulating factor; Proliferation-induced ligands

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前言

急性淋巴细胞白血病是临床上常见的血液系统肿瘤之一，它是一种恶性肿瘤，起源于骨髓淋巴细胞的 B 系列或 T 系列细胞异常增殖。儿童为该病的高发人群，占白血病 70%以上，根据疾病的不同生物学特征制定治疗方案已取得不错的效果，使大部分患者获得长期无病生存，且有治疗的可能[1,2]。有研究显示，BAFF、APRIL 在淋巴细胞广泛表达，在多种血液系统疾病

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作者简介：王瑾（1981-），女，博士，主治医师，研究方向：血液肿瘤免疫治疗的机制研究，

电话：18092560180，E-mail：zhangxianchao8234@163.com

△ 通讯作者：马肖容（1970-），女，博士，主任医师，研究方向：血液病学专业，电话：029-87679457

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中表达增高[3,4]。甲氨蝶呤是治疗急性淋巴细胞白血病的常用化疗药物，能通过抑制二氢叶酸还原酶，可以阻断肿瘤细胞的合成，抑制肿瘤细胞的生长和繁殖，对提高急性淋巴细胞白血病长期无病生存率具有非常重要的意义，但目前临床上关于其对BAFF、APRIL影响的相关报道较少[5,6]。因此，本研究旨在探讨甲氨蝶呤治疗急性淋巴细胞白血病的疗效，并观察其对BAFF、APRIL的影响，现报道如下。

1 资料与方法

1.1 一般资料

选择2016年8月至2018年9月我院收治的急性淋巴细胞白血病患者50例进行研究。采用随机分组法分为2组，观察组26例，其中男14例，女12例；年龄19-65岁，平均48.69±6.15)岁，病程1~6年，平均(3.25± 0.35)年。对照组24例，男13例，女11例；年龄20~66岁，平均(48.73± 6.24)岁，病程1.5~6年，平均(3.21± 0.37)年。两组基线资料无明显差异，具有可比性。

纳入标准：(1) 符合《成人急性淋巴细胞白血病的诊疗进展》[7]中的诊断标准；(2)年龄＞18岁；(3)化疗耐受者。排除标准：(1)心功能异常者；(2)复发性白血病；(3)合并恶性肿瘤者。(4)合并严重感染疾病。

1.2 方法

两组患者均给予营养支持、预防感染等常规治疗。对照组在此基础上进行化疗，方案如下：长春瑞滨(规格10 mg，厂家：江苏豪森药业集团有限公司，国药准字H20041105)30 mg静脉滴注；吡柔比星(规格10 mg，厂家：海正辉瑞制药有限公司，国药准字H20045983)40 mg静脉滴注；门冬酰胺酶(规格5000单位，厂家：北京双鹭药业股份有限公司，国药准字H20057369)5000 IU/m^2。观察组给予甲氨蝶呤：甲氨蝶呤(规格0.1 g，厂家：江苏恒瑞医药股份有限公司，国药准字H32026443)3 g/m^2/d，1d1次。

1.3 观察指标

采集治疗前、后肘静脉血4 mL，3500 r·min^{-1}离心10 min，提取血清，采用酶联免疫吸附试验(ELISA)测定BAFF、APRIL水平；采用全自动流式细胞仪测定CD4$^+$、CD8$^+$、CD4$^+$/CD8$^+$水平；观察记录不良反应发生情况。

疗效评定标准：显效：症状消失，血象恢复正常，原始粒细胞≤ 0.05；有效：症状有所改善，血象有所改善；无效：无明显改善或加重。

1.4 统计学分析

以spss18.0软件包处理，符合正态分布计量资料用均数±标准差($\bar{x}\pm s$)表示，组间比较使用独立样本t检验，计数资料以率表示，x^2检验，P＜0.05表示差异具有统计学意义。

2 结果

2.1 两组疗效比较

观察组总有效率84.62%显著高于对照组58.33%，差异显著(P＜0.05)，见表1。

表1 两组疗效比较[n(%)]

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

Groups	n	Excellent	Effective	Invalid	Total effective rate
Observation group	26	12(46.15)	10(38.46)	4(15.38)	22(84.62)
Control group	24	8(33.33)	6(25.00)	10(41.67)	14(58.33)
x^2 value					4.273
P value					0.039

2.2 两组BAFF、APRIL水平比较

治疗前，两组BAFF、APRIL水平无显著差异(P>0.05)；治疗后，两组BAFF、APRIL水平均显著下降，且观察组低于对照组(P<0.05)，见表2。

表2 两组BAFF、APRIL水平比较($\bar{x}\pm s$)

Table 2 Comparison of BAFF and APRIL levels between the two groups($\bar{x}\pm s$)

Groups	n	BAFF(pg/mL)		APRIL(ng/mL)	
		Before the treatment	After treatment	Before the treatment	After treatment
Observation group	26	450.79± 63.21	280.16± 30.14	31.46± 5.04	18.46± 2.21
Control group	24	451.08± 63.53	309.69± 35.68	31.28± 5.32	24.73± 3.78
t value		0.016	3.169	0.123	7.228
P value		0.987	0.003	0.903	0.000

2.3 两组T淋巴细胞亚群水平比较

治疗前，两组T淋巴细胞亚群水平无显著差异(P>0.05)；治疗后，两组T淋巴细胞亚群水平均显著改善，且观察组CD4$^+$、CD4$^+$/CD8$^+$高于对照组，CD8$^+$低于对照组(P<0.05)，见表3。

2.4 两组不良反应比较

两组患者不良反应发生情况均无统计学意义(P>0.05)，见表4。

表 3 两组 T 淋巴细胞亚群水平比较($\bar{x}\pm s$)

Table 3 Comparison of T lymphocyte subsets between the two groups($\bar{x}\pm s$)

Groups	n	$CD4^+$(%)		$CD8^+$(%)		$CD4^+/CD8^+$	
		Before the treatment	After treatment	Before the treatment	After treatment	Before the treatment	After treatment
Observation group	26	43.57± 6.12	58.97± 8.31	52.71± 7.01	43.56± 6.12	0.82± 0.12	1.29± 0.15
Control group	24	43.61± 6.09	51.35± 7.31	52.69± 7.05	50.01± 7.12	0.81± 0.14	1.01± 0.14
t value		0.023	3.431	0.010	3.443	0.272	6.808
P value		0.982	0.001	0.992	0.001	0.787	0.000

表 4 两组不良反应比较[n(%)]

Table 4 Comparison of adverse reactions between the two groups[n(%)]

Groups	n	Oral mucosa damage	Impairment of liver function	Infection	Bone marrow suppression	Gastrointestinal reaction
Observation group	26	6(23.08)	5(19.23)	4(15.38)	11(42.31)	8(30.77)
Control group	24	8(33.33)	6(25.00)	6(25.00)	12(50.00)	9(37.50)
x^2 value		0.651	0.242	0.721	0.297	0.252
P value		0.419	0.623	0.396	0.586	0.616

3 讨论

急性淋巴细胞白血病是由于造血干细胞在分化为淋巴细胞的过程发生恶性增殖,抑制正常造血,并浸润肝、脾、淋巴结组织造成的[8,9]。该病起病急,临床表现为贫血、出血、感染及浸润表现,临床通常使用化疗、免疫治疗等治疗急性淋巴细胞白血病,其中儿童急性淋巴细胞白血病 5 年无病生存率已超过 80%,但仍有部分患者存在复发[10-13]。

部分患者由于高度耐药而复发,因此选择合适的治疗方案对疾病具有重要意义[14,15]。甲氨蝶呤是一种与二氢叶酸还原酶结合,防止二氢叶酸转化为四氢叶酸的叶酸代谢物,抑制脱氧核糖核酸合成,从而发挥抗肿瘤的作用[16,17]。有研究显示,甲氨蝶呤治疗急性淋巴细胞白血病已有近 50 年的历史,且取得了不错的疗效[18]。本研究结果显示,使用甲氨蝶呤治疗的患者临床总有效率明显高于使用常规化疗治患者,提示,甲氨蝶呤可提高急性淋巴细胞白血病的治疗效果,与 Kathiravan M [19]等研究结果相似。

较多研究显示,BAFF、APRIL 在调节淋巴细胞分化和成熟中具有重要作用,二者协同表达时,参与 B、T 细胞的调节和骨髓微环境的维持[20-22]。BAFF 由单核细胞、树突状细胞及 T 细胞产生,是骨髓细胞及浆母细胞存活的必要因子之一,在免疫应答中起重要作用[23,24]。有研究显示,其水平在多种血液系统和自身免疫性疾病中水平显著升高[25]。APRIL 是肿瘤坏死因子家族的新成员,能促进肿瘤细胞增殖,在 T、B 淋巴细胞的成熟和活化中起重要作用[26,27]。DeRenzo C [28]等研究发现,儿童急性淋巴细胞白血病患儿 APRIL 表达升高,与儿童急性淋巴细胞白血病的发生密切相关。本研究结果显示,治疗后患者 BAFF、APRIL 水平均显著下降,且使用甲氨蝶呤治疗的患者低于对照组,与 Paz H [29]等研究结果相似。分析其原因是因为甲氨蝶呤可通过细胞膜上还原型叶酸盐载体及被动转运方式进入细胞内,可使血清白蛋白变性,成为具有免疫原性的载体蛋白,而 BAFF、APRIL 具有可溶型,可溶性蛋白可以增强 B 细胞、$CD4^+$ 细胞,通过增加免疫应答改善患者 BAFF、APRIL 水平。Anita Vallacha [30]等研究显示,甲氨蝶呤可改善急性淋巴细胞白血病患者的免疫功能。本研究结果也显示,治疗后患者 T 淋巴细胞亚群水平均显著改善,且使用甲氨蝶呤治疗的患者 $CD4^+$、$CD4^+/CD8^+$ 高于对照组,$CD8^+$ 低于对照组,提示,甲氨蝶呤可改善急性淋巴细胞白血病患者 T 淋巴细胞亚群水平,提高患者的免疫功能。分析其原因是因为甲氨蝶呤可抑制淋巴细胞生长,降低 T 淋巴细胞水平,从而提高患者的免疫功能。此外,研究结果也显示,两组患者不良反应发生情况均无统计学意义,说明甲氨蝶呤并不会显著增加患者不良反应的发生,可能是与甲氨蝶呤的浓度和时间有关,后期可考虑控制其输注时间及药物浓度,以降低不良反应的发生。

综上所述,在急性淋巴细胞白血病患者中应用甲氨蝶呤效果显著,可有效改善患者 BAFF、APRIL 水平。

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