doi: 10.13241/j.cnki.pmb.2015.18.016

中药联合化疗对 ALL 患者 CD4、CD25 细胞调节及 sE-cad 的影响 *

方 阅[1] 张 渊[1] 方 敏[1] 刘皋林[1△] 白利民[2]

（1 上海交通大学附属第一人民医院 上海 200080；2 南京中医药大学临床学院 江苏 南京 210046）

摘要 目的：研究中药联合化疗方案对急性淋巴细胞白血病（Acute lymphocytic leukemia, ALL）患者 $CD4^+$、$CD25^+$ 细胞调节的影响、血清 sE-cad 的影响以及临床意义。**方法：**选取我院血液科收治的急性淋巴细胞白血病患者 60 例，随机分为两组，其中对照组 30 例给予常规化疗方案治疗，中药组 30 例在常规化疗方案的基础上加用中药辅助治疗。对比治疗前后患者血常规、$CD4^+$、$CD25^+$ 细胞及血清 sE-cad 的改变。**结果：**①治疗后两组患者 $CD4^+$、$CD25^+$T 细胞较治疗前均显著下降，差异有统计学意义（P＜0.05），与对照组相比，中药组 $CD4^+$、$CD25^+$T 细胞下降明显，差异有统计学意义（P＜0.05）；②治疗后两组患者血清 sE-cad 均改善，且中药组（55.58± 10.47）较对照组（67.27± 11.32）明显下降，差异有统计学意义（P＜0.05）；③两组有效率比较重，中药组总有效率（86.67 %）明显优于对照组（66.67 %），差异有统计学意义（P＜0.05）。**结论：**中药联合化疗治疗急性淋巴细胞白血病 $CD4^+$、$CD25^+$T 细胞调节及血清 sE-cad 的改变明显，对临床具有指导意义。

关键词：中药；血清 sE-cad；$CD4^+$；$CD25^+$

中图分类号：R733.7 **文献标识码：**A **文章编号：**1673-6273(2015)18-3466-04

Effect of Traditional Chinese Medicine Combined with Chemotherapy for Patients with ALL CD4, the Regulation of CD25 Cell and sE-cad*

FANG Yue[1], ZHANG Yuan[1], FANG Min[1], LIU Gao-lin[1△], BAI Li-min[2]

(1Department of Pharmacy, First People is Hospital of Shanghai, Shanghai, 200080, China; 2 Department of Hematology, Clinical College of Nanjing University of Chinese Medicine, Jiangsu, Nanjing, 210046, China)

ABSTRACT Objective: To study traditional Chinese medicine combined with chemotherapy for acute lymphoblastic leukemia (Acute lymphocytic leukemia, ALL) in patients with $CD4^+$, $CD25^+$ cell regulation effect, serum sE-cad and the effect of clinical significance. **Methods:** 60 patients with acute lymphoblastic leukemia in our hospital chosen from the Department of Hematology were randomly divided into two groups; 30 patients in control group received conventional chemotherapy treatment, 30 cases of the Chinese medicine group were treated by traditional Chinese medicine auxiliary based on conventional chemotherapy. Change the blood routine test, $CD4^+$, $CD25^+$ cells and serum sE-cad before and after treatment were compared. **Results:** After treatment, patients in the two groups with $CD4^+$, $CD25^+$T cells were significantly lower than that before treatment, and the difference was statistically significant (P < 0.05); compared with the control group, $CD4^+$, $CD25^+$T cells, the Chinese medicine group decreased significantly, and the difference was statistically significant (P < 0.05); after the treatment , serum sE-cad of the two groups of patients were both improved, and decreased significantly in the traditional Chinese medicine group (55.58 + 10.47) than in the control group (67.27 + 11.32), and the difference was statistically significant (P < 0.05); the two group's efficiency is relatively heavy, total effective rate of the traditional Chinese medicine group(86.67%) was significantly better than that of the control group (66.67%), and the difference was statistically significant (P < 0.05). **Conclusion:** Traditional Chinese medicine combined with chemotherapy in the treatment of acute lymphoblastic leukemia $CD4^+$ and $CD25^+$T cells modulate and serum sE-cad change significantly, has the guidance significance for clinical.

Key words: Chinese traditional medicine; serum sE-cad; $CD4^+$; $CD25^+$

Chinese Library Classification(CLC): R733.7 Document code: A

Article ID:1673-6273(2015)18-3466-04

前言

急性淋巴细胞性白血病（acute lymphoblastic leukemia，ALL）是指存在于血液、骨髓、淋巴结、脾脏等器官中，类似于淋巴母细胞的未成熟白细胞为特征的一种进行性恶性疾病[1]。中医可归属为＂虚劳＂、＂血证＂等范畴[2]。依据细胞形态学以及预后情况的差异，临床分为 L1，L2，L3 三个亚型，主要以发热、贫血或出血为首发症状。急性淋巴细胞性白血病起病较急，进程迅速，也有部分患者起病较缓，主要表现为进行性贫血[3]。ALL 在成年人及儿童中的发病率分别占急性白血病的 20 %和

* 基金项目：国家自然科学基金项目（H0136）

作者简介：方阅，女，本科，主要研究方向：药物基础与临床研究

△通迅作者：刘皋林，男，博士，主要研究方向：药物基础与临床研究

（收稿日期：2014-12-14 接受日期：2014-12-30）

80 %。在急性白血病中,恶性细胞迅速分裂,取代正常的骨髓成分,导致骨髓衰竭[4]。由于正常细胞数目的减少,患者易发生出血和感染等情况。相关病例分析发现,多数 ALL 并未存在明显诱因,部分以辐射、某些化学试剂、毒素和异常的染色体病变为诱因,在急性白血病的发生过程中发挥一定的作用[5]。当今医学主要以化疗为治疗手段,但在化疗尤其随着剂量加大及疗程延长的同时,往往无法避免大量药物毒副作用的发生,使患者出现极大不便。我们采用中药联合化疗方案治疗急性淋巴细胞白血病,观察中药联合化疗方案对患者 $CD4^+$、$CD25^+$ 细胞调节的影响以及血清 sE-cad 的改变,为急性白血病治疗提供新的思路。

1 资料与方法

1.1 一般资料

选取 2012 年 4 月至 2014 年 5 月于我院以急性淋巴细胞白血病为诊断而收入院患者 60 例,采用随机数字表分为中药组和对照组。中药组 30 例,其中男 18 例,女 12 例,年龄 15-63 岁,平均年龄 33.5± 15.3 岁;对照组 30 例,其中男 16 例,女 14 例,年龄 14-65 岁,平均年龄 34.7± 16.8 岁。症状:发热、贫血、出血倾向等。体征:肝、脾、淋巴结肿大;骨关节疼痛,胸骨压痛;部分男性患者,睾丸受累可呈弥漫性肿大。两组患者的一般资料相仿,差异无统计学意义(P> 0.05)。患者自愿参与本实验,并签署知情同意书。

1.2 纳入及排除标准

纳入标准:①年龄在 14-65 岁;②符合上述诊断标准;③依从性良好,积极配合治疗、复查者。排除标准:①年龄 <14 岁或年龄 >65 岁;②严重肝、胆疾病者;③妊娠及哺乳期妇女;④恶性肿瘤,合并严重感染者;⑤心、肝、肾功能不全者;⑥血液、内分泌系统疾病者;⑦神志异常以及无法配合治疗、复查者。

1.3 治疗方法

对照组给予常规化疗方案 VDLP。VDLP 方案:长春新碱 2 mg,静注 d1、7、14;柔红霉素 30 mg/m²/d,静注 d1-3、11-14;左旋门冬酰胺酶 10000 u,静点 d1-7;泼尼松 1 mg/kg,口服 d1-14。中药组在对照组常规化疗方案的基础上自治疗之日起加用同步口服中药,中药组方原则:扶正抗癌、解毒化瘀;中药组成生黄芪 30 g,生白术 12 g,生薏仁 30 g,冰球子 24 g,莪术 12 g,七叶一枝花 24 g,女贞子 12 g,姜黄 9 g,天龙 6 g,仙灵脾 12 g ,日一剂水煎服,早晚两次温服,每次 50 mL。注意事项:用药期间,禁食生冷辛辣等刺激性食物,戒烟酒,保持患者情绪稳定。分别于化疗前及化疗后第 14 天检查患者尿常规、便常规、肝功、肾功、心电图、血常规、$CD4^+$、$CD25^+$ 细胞及血清 sE-cad。

1.4 疗效判定

1.4.1 西医疗效判定标准 参照《血液病诊断及疗效标准》[6]:完全缓解(CR):①由细胞浸润所致的白血病症状、体征消失,完全或基本恢复正常生活;②血象:男性 Hb≥ 100 g/L,女性及儿童≥ 90 g/L,中性粒细胞绝对值≥ 1.5× 10^9/L,血小板≥ 100× 10^9/L。外周血白细胞分类中无白血病细胞;部分缓解(PR):临床症状或血象分析中有 1 项未完全达标者;无效(NR)或复发:由细胞浸润所致的白血病症状、体征没有消失甚或加重。

1.4.2 中医证候疗效判定标准 参照《中药新药临床研究指导原则》[7],痊愈:临床症状、体征完全或基本消失,积分减少≥ 90 %;显效:症状、体征明显改善,70 %≤ 积分减少 <90 %;有效:症状、体征均有所好转,30%≤ 积分减少 <70%;无效:症状、体征均无明显改善,甚加重,积分减少不足 30 %。治疗有效率 =[(治疗前积分 - 治疗后积分)÷ 治疗前积分]× 100 %。

1.5 统计学方法

采用统计学软件 SPSS19.0 进行统计学分析,数据以均数± 标准差($\bar{x}$± s)表示,计量资料采用 t 检验,计数资料采用卡方检验处理,以 P< 0.05 为差异显著,有统计学意义。

2 结果

2.1 $CD4^+$ 与 $CD25^+$T 细胞调节的变化

治疗前两组患者患者 $CD4^+$、$CD25^+$ 细胞比例比较无统计学差异;治疗后两组患者 $CD4^+$、$CD25^+$ 细胞比例较治疗前下降,差异有统计学意义,P< 0.05;与对照组比较,实验组患者 $CD4^+$、$CD25^+$ 细胞比例下降显著,差异有统计学意义(P< 0.05)。表 1。

表 1 治疗前后 $CD4^+$、$CD25^+$ 细胞水平的变化比较

Table 1 Comparison of the changes of $CD4^+$, $CD25^+$ cell levels before and after treatment between two groups

Group		$CD4^+$ cells (%)	$CD25^+$cells (%)
Chinese medicine group	Before treatment	5.84± 1.96	7.14± 0.21
	After treatment	3.23± 1.78△*	4.16± 0.25△*
Control group	Before treatment	5.81± 1.94	7.03± 0.19
	After treatment	4.42± 1.81△	5.58± 0.54△

Note:△P<0.05,compared with before treatment;*P<0.05,compared with control group

2.2 血清 sE-cad 的改变情况比较

如表 2 结果显示,两组患者血清 sE-cad 在治疗前无明显差异,没有统计学意义,具有可比性。与治疗前比较,经治疗后中药组和对照组两组血清 sE-cad 均有显著改变,具有显著的统计学意义(P< 0.05)。治疗后两组间比较,中药组 sE-cad (26.58± 10.47)ng/mL 要优于对照组 (35.27± 11.32)ng/mL,差异有统计学意义(P< 0.05)。

2.3 治疗结束后两组疗效比较

中药组 30 例患者中 CR、PR、NR 患者分别为 22、4、4 例,对照组 30 例患者中 CR、PR、NR 患者分别为 13、7、10 例,中药

组和对照组两组总有效率分别为 86.67 %和 66.67 %，中药组疗效要优于对照组，差异有统计学意义（P＜0.05），如表 3。

表 2 治疗前后血清 sE-cad 的改变情况比较（$\bar{x}\pm s$）

Table 2 Comparison of changes of serum sE-cad before and after treatment($\bar{x}\pm s$)

Group		sE-cad(ng/mL)
Chinese medicine group	Before treatment	84.56± 23.35
	After treatment	55.58± 10.47△*
Control group	Before treatment	83.45± 22.64
	After treatment	67.27± 11.32△

Note:△P<0.05, compared with before treatment; *P<0.05, compared with control group.

表 3 两组患者疗效比较

Table 3 Comparison of curative effect between two groups

Group	n	CR	PR	NR	Total efficacy
Chinese medicine group	30	22	4	4	86.67 %△
Control group	30	13	7	10	66.67 %
P	-	-	-	-	0.032
X^2	-	-	-	-	44.2173

Note: △P<0.05, compared with control group.

3 讨论

白血病在全国各种恶性肿瘤的排名中位列前十位，死亡率极高[8]。急性白血病是一种最常见的恶性克隆性造血系统疾病，其显著特征为白血病细胞过度增殖及受抑调亡[9]。目前，急性白血病仍以细胞杀伤、分化及凋亡为主要缓解治疗方法，但因不能有效缓解或复发而导致死亡率常年居高不下[10]。为提高急性白血病的缓解率，降低其复发率，国内外首选大剂量化疗药物联合应用的方案[11-13]。但相关研究显示，其毒副作用会随着化疗药物剂量的增加而显著增多[14,15]。

中药在我国具有着悠久的历史，毒副作用较小，在治疗恶性肿瘤方面别具功效，以中西医结合防治肿瘤为特色，受到国内外广泛关注[16]。中医理念认为，药物的毒副作用以毒素侵袭肝肾，致肝肾亏虚、脾胃气血耗伤为主要表现。因此，中医临床常以扶正祛邪、补益肝肾气血为肿瘤治疗的基本原则[17-19]。相关研究表明砒霜、雄黄等中药在急性早幼粒细胞白血病的治疗上疗效显著，已广泛投入临床治疗。本研究通过对中药联合化疗治疗急性淋巴细胞白血病的临床疗效进行研究，探讨其临床应用意义。研究表明中药复方抗肿瘤作用可以通过多条途径实现，如直接杀伤肿瘤细胞；诱导肿瘤细胞凋亡、影响癌基因和抑癌基因的表达；抑制肿瘤血管形成、改变血液流变学异常、影响端粒酶活性；多途径、多层面对免疫系统发挥调节作用或抑制肿瘤血管形成等，本文则从 $CD4^+$、$CD25^+$T 细胞及血清 sE-cad 角度进行论证。

本研究结果显示，治疗后中药组和对照组两组患者 $CD4^+$、$CD25^+$T 细胞均发生显著改变，差异有明显的统计学意义（P＜0.05）；与治疗前比较，中药组和对照组两组患者经治疗后血清 sE-cad 均有显著改变（P＜0.05）；治疗后两组间比较，中药组指标明显优于对照组（P＜0.05）。两组治疗效果比较，中药组总有效率为 86.67 %，明显优于对照组 66.67 %（P＜0.05）。结果说明，中药联合化疗治疗急性淋巴细胞白血病具有更佳的临床疗效。以半枝莲、生薏仁、山慈菇等为主的复方中药在临床上用于治疗肝癌、肺癌、乳腺癌都有一定的疗效，中药进入机体后发挥作用的情形与之在体外肿瘤细胞系中的作用不尽相同，中药复方可以激活 T 细胞、B 细胞、NK 细胞等免疫细胞的活性，促进包括 $CD4^+$、$CD25^+$ 在内的多种细胞因子的生，促进抗体和补体的生成，从而提高机体抗肿瘤的免疫力[20]。但本研究受临床条件、时间等外因限制，因样本含量范围较局限，致使某些数据的证明力度不强，望在今后的研究中进一步扩大样本量，加强各项指标的科学完整性，缩小误差。

综上所述，中药联合化疗能明显改善急性淋巴细胞白血病患者的生存质量，在增加化疗药物治疗作用的同时有效降低化疗药物的毒副作用，提高机体抗感染力，值得临床推广应用。

参 考 文 献(References)

[1] Lee MY, Liu YW, Chen MH. Indirubin-3'-monoxime promotes autophagic and apoptotic death in JM1 human acute lymphoblastic leukemia cells and K562 human chronic myelogenous leukemia cells [J]. Oncology reports, 2013, 29(5): 2072-2078

[2] Fuchs O. Transcription factor NF-κB inhibitors as single therapeutic agents or in combination with classical chemotherapeutic agents for the treatment of hematologic malignancies [J]. Current molecular pharmacology, 2010, 3(3): 98-122

[3] Zhang W, Dai BT, Xu YH. Effects of matrine on invasion and metastasis of leukemia cell line Jurkat [J]. Chinese journal of integrated traditional and Western medicine, 2011, 28(10): 907-911

[4] Backhus LM, Farjah F, Varghese TK. Appropriateness of imaging for lung cancer staging in a national cohort [J]. Journal of clinical oncology, 2014, 32(30): 3428-3435

[5] Sullivan I, Salazar J, Majem M. Pharmacogenetics of the DNA repair

pathways in advanced non-small cell lung cancer patients treated with platinum-based chemotherapy[J]. Cancer letters, 2014, 353(2): 160-166

[6] Yamaguchi M, Sugio K. Current status of induction treatment for N2-Stage III non-small cell lung cancer [J]. General thoracic and cardiovascular surgery, 2014, 62(11): 651-659

[7] Li XS, Fan HX, Fang H. Value of Whole-Tumor Dual-Input Perfusion CT in Predicting the Effect of Multiarterial Infusion Chemotherapy on Advanced Non-Small Cell Lung Cancer [J]. American journal of roentgenology, 2014, 203(5): W497-505

[8] Jorge SE, Kobayashi SS, Costa DB. Epidermal growth factor receptor (EGFR) mutations in lung cancer: preclinical and clinical data [J]. Brazilian journal of medical and biological research, 2014, 47(11): 929-939

[9] Qian LR, Fu W, Shen JL. Agents for refractory/relapsed acute lymphocytic leukemia in adults [J]. European review for medical and pharmacological sciences, 2014, 18(17): 2465-2474

[10] Benites EC, Cabrini DP, Silva AC. Acute respiratory viral infections in pediatric cancer patients undergoing chemotherapy [J]. Jornal de pediatria, 2014, 90(4): 370-376

[11] Niewerth D, Jansen G, Riethoff LF. Antileukemic activity and mechanism of drug resistance to the marine Salinispora tropica proteasome inhibitor salinosporamide A (Marizomib) [J]. Molecular pharmacology, 2014, 86(1): 12-19

[12] Valkovi¡ T, Seili-Bekafigo I, Ba¸i¡-Kinda S. Therapy-related acute myeloblastic leukemia after splenectomy in a patient with composite lymphoma developing after treatment of chronic lymphocyticleukemia[J]. Annals of hematology, 2014, 93(6): 1057-1059

[13] Saleh AJ, Alhejazi A, Ahmed SO. Leukemia during pregnancy: long term follow up of 32 cases from a single institution [J]. Hematology, 2014, 7(2): 63-68

[14] Kojima K, Ando T, Kimura S. Molecular targeted therapy in lymphoid leukemias[J]. Nihon rinsho, 2014, 72(6): 1094-1098

[15] Bonanthaya R, Appaji L, Lakshmaiah KC. A child with acute lymphocytic leukaemia[J]. Malawi medical journal, 2014, 26(2): 51-52

[16] Niscola P, Ragusa D, Scaramucci L. Unexplained severe Coombs-negative hemolytic anemia during treatment of refractory chronic lymphocytic leukemia with alemtuzumab [J]. Annals of hematology, 2014, 93(5): 863-865

[17] Wang J, Zhang BH, Xue HM. Hyperglycemia during chemotherapy influences the prognosis of children with acute lymphocytic leukemia [J]. Journal of experimental hematology, 2014, 22 (1): 69-72

[18] Zeng DF, Zhang J, Zhu LD. Analysis of drug resistance-associated proteins expressions of patients with the recurrent of acute leukemia via protein microarray technology [J]. European review for medical and pharmacological sciences, 2014, 18(4): 537-543

[19] Morais EF, Lira JA. Oral manifestations resulting from chemotherapy in children with acute lymphoblastic leukemia[J]. Brazilian journal of otorhinolaryngology, 2014, 80(1): 78-85

[20] Azimi F, Jafariyan M, Khatami S. Assessment of Thiopurine-based drugs according to Thiopurine S-methyltransferase genotype in patients with Acute Lymphoblastic Leukemia [J]. Iranian journal of pediatric hematology and oncology, 2014, 4(1): 32-38

（上接第 3442 页）

[14] Toh Y, Pencil SD, Nicolson GL.A novel candidate metastasis-associated gene, mta1, differentially expressed in highly metastatic mammary adenocarcinoma cell lines. cDNA cloning, expression, and protein analyses[J]. J Biol Chem,1994, 269(37): 22958-22963

[15] Marzook H, Li DQ, Nair VS, et al. Metastasis-associated protein 1 drives tumor cell migration and invasion through transcriptional repression of RING finger protein 144A [J]. J Biol Chem, 2012, 287 (8): 5615-5626

[16] Pakala SB, Rayala SK, Wang RA, et al. MTA1 promotes STAT3 transcription and pulmonary metastasis in breast cancer [J]. Cancer Res, 2013, 73(12): 3761-3770

[17] Jiang Q, Zhang H, Zhang P. ShRNA-mediated gene silencing of MTA1 influenced on protein expression of ER alpha, MMP-9, CyclinD1 and invasiveness, proliferation in breast cancer cell lines MDA-MB-231 and MCF-7 in vitro [J]. J Exp Clin Cancer Res, 2011, 30: 60

[18] Yoo YG, Kong G, Lee MO. Metastasis-associated protein 1 enhances stability of hypoxia-inducible factor-1alpha protein by recruiting histone deacetylase 1[J]. EMBO J, 2006, 25(6): 1231-1241

[19] Chen S, Dong Y, Xu C, et al. Involvement of a chromatin modifier in response to mono-(2-ethylhexyl) phthalate (MEHP)-induced Sertoli cell injury: probably an indirect action via the regulation of NFkappaB/FasL circuitry [J]. Biochem Biophys Res Commun,2013, 440(4): 749-755

[20] Li DQ, Ohshiro K, Khan MN, et al. Requirement of MTA1 in ATR-mediated DNA damage checkpoint function [J]. J Biol Chem, 2010, 285(26): 19802-19812

[21] Wang RA. MTA1--a stress response protein: a master regulator of gene expression and cancer cell behavior [J]. Cancer Metastasis Rev, 2014, 33(4): 1001-1009