

doi: 10.13241/j.cnki.pmb.2014.36.021

沙利度胺配合化疗应用于急性白血病患者疗效评价*

陈 亨 蒋元强 杨国华 沈云峰 周 新

(南京医科大学附属无锡市人民医院血液科 江苏 无锡 214000)

摘要 目的:探究急性白血病患者给予沙利度胺配合化疗在抗血管生长方面的临床成效。**方法:**选取我院 2009 年 3 月-2014 年 1 月收治的 86 例急性白血病患者,随机分为研究组和对照组,每组 43 例。对照组患者给予常规化疗方案,研究组在对照组基础上给予沙利度胺配合化疗。观察两组患者治疗前后血浆 VEGF、VEGFR、bFGF 及 MVD 的水平变化。比较两组患者的临床疗效及不良反应发生率。**结果:**治疗前,两组患者 VEGF、VEGFR、bFGF 及 MVD 水平无显著差异($P>0.05$);治疗后,研究组患者 VEGF、VEGFR、bFGF 及 MVD 水平均低于对照组,差异有统计学意义($P<0.05$)。研究组患者治疗的有效率为 88.4%,对照组为 76.7%,研究组显著优于对照组,差异具有统计学意义($P<0.05$)。研究组不良反应发生率为 79.1%,对照组为 81.4%,差异无统计学意义($P>0.05$)。**结论:**沙利度胺配合化疗治疗急性白血病能调控促血管生长因子水平,提高疗效,不良反应可耐受。

关键词:沙利度胺;急性白血病;抗血管生成

中图分类号:R733.71 文献标识码:A 文章编号:1673-6273(2014)36-7079-04

Efficacy of Thalidomide Combined with Chemotherapy on Acute Leukemia*

CHEN Heng, JIANG Yuan-qiang, YANG Guo-hua, SHEN Yun-feng, ZHOU Xin

(Department of Hematology, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu, 214000, China)

ABSTRACT Objective: To explore the clinical effect of thalidomide combined with chemotherapy in antiangiogenesis of acute leukemia patients. **Methods:** 86 cases of acute leukemia were selected, who were treated in our hospital from March 2009 to January 2014 and randomly divided into the study group and the control group with 43 cases in each group. The patients in the control group received conventional chemotherapy, while the patients in the study group were given thalidomide combined with chemotherapy. Then the levels of VEGF, VEGFR, bFGF and MVD in plasma of patients were observed and compared before and after the treatment, and the clinical effect and the adverse reactions were compared between the two groups. **Results:** There was no statistically significant difference between the two groups about the VEGF, VEGFR, bFGF and MVD before treatment ($P>0.05$); the levels of VEGF, VEGFR, bFGF and MVD in the study group were lower than those of the control group after the treatment with statistically significant difference($P<0.05$). The efficiency rate was 88.4 % in the study group which was higher than 76.7 % in the control group with statistical significance ($P<0.05$). There was no statistically significant difference between the two groups in the adverse events ($P>0.05$). **Conclusion:** Thalidomide combined with chemotherapy compared with chemotherapy alone in acute leukemia, can regulate the angiogenic growth factor level, and the adverse reactions were acceptable.

Key words: Thalidomide; Acute leukemia; Antiangiogenesis

Chinese Library Classification(CLC):R733.71 **Document code:** A

Article ID:1673-6273(2014)36-7079-04

前言

急性白血病是造血干细胞恶性克隆所致,一旦发病会引起骨髓中的幼稚细胞及原始细胞大量增殖而破坏机体正常造血功能,进而导致异常血细胞浸润肝脏、脾脏及淋巴结组织^[1,2]。该病症临床表现为重度贫血、感染及出血等,若不及时给予对症治疗,则危及生命,但有患者经综合治疗后病情得以缓解,可延长生存年限^[3]。随着环境中电磁辐射强度及范围的加大,急性白血病发病率呈现逐年攀升之势。近年来相关研究发现,急性白血病的病情进展与新生血管大量增殖密切相关^[4]。异常血细胞的增殖会影响机体内分泌系统代谢功能,导致机体激素水平紊

乱,进而激活白血病细胞分泌大量的血管内皮生长因子(VEGF)、碱性成纤维细胞生长因子(bFGF)等血管生长调控因子^[5,6]。

目前治疗白血病方法较多,而如何快速抑制新生血管形成则是当前治疗白血病的新型目标,已成为国内外专家关注的重点^[7]。据文献指出,沙利度胺联合化疗方案治疗白血病具有良好的临床效果^[8]。为了进一步验证该药物配伍经典化疗方案的临床疗效。我们进行了相关研究,现报道如下。

1 资料与方法

1.1 一般资料

* 基金项目:国家自然科学基金项目(81170490)

作者简介:陈亨(1983-),男,主治医师,博士研究生,研究方向:血液科疾病的诊断与治疗

(收稿日期:2014-07-04 接受日期:2014-07-29)

选取我院血液科于 2009 年 3 月~2014 年 1 月收治的 86 例急性白血病患者,其中男 59 例,女 27 例,年龄 19~72 岁,平均(48.3±7.0)岁。所有患者入院均经骨髓穿刺活检、骨髓细胞学、免疫分型及染色体检查,再联合其临床症状体征,确诊为急性白血病,诊断参照人卫第 7 版《内科学》教材中关于该病的诊

断标准。纳入标准:患者无其他心、肝、肾等重要脏器疾病;无任何精神或心理方面疾病;无自身免疫系统疾病;对本研究知悉并签署同意书。利用随机数字表法进行分组,分别设为研究组和对照组,每组各 43 例。两组在性别、年龄、白血类别方面差异无统计学意义($P>0.05$),具有可比性。见表 1。

表 1 两组患者基线资料比较(例)
Table 1 Comparison of baseline data (cases) between the two groups

Group	N	Gender (M/ F)	Age (Year)	Acute myeloid leukemia				Acute lymphocytic leukemia		
				M2	M3	M4	M5	L1	L2	L3
Study group	43	30/13	47.6± 6.9	10	12	9	12	15	13	15
Control group	43	29/14	49.0± 7.2	11	11	10	11	14	14	15
t or X^2	—	$X^2=1.368$	$t=0.478$		$X^2=1.246$				$X^2=1.092$	
P	—	>0.05	>0.05		>0.05				>0.05	

1.2 方法

对照组:本组患者给予常规化疗方案,即对于急性髓细胞白血病患者采用柔红霉素联合阿糖胞苷治疗,急性淋巴细胞白血病给予长春新碱、吡柔比星、环磷酰胺联合泼尼松化疗,对于 M3 型急性髓细胞白血病患者则给予全反式维甲酸联合三氧化二砷治疗。化疗方案持续 4 个月。研究组:本组患者在对照组基础上给予沙利度胺治疗,其具体用药方案为:50 mg/d,口服用药,持续给药 4 个月。两组患者在治疗期间根据其表现出的具体不良反应予以对症处理,包括抗感染、输注血液制品及支持疗法。

1.3 观察项目

①记录两组患者临床疗效。按照《血液病诊断与疗效标准》(第 3 版)^[9]进行疗效评定,划分为完全缓解、部分缓解及未缓解。有效率(%)=本组(完全缓解+部分缓解)例数/本组研究总例数×100%。②记录两组患者治疗前及治疗后第 8 w 末血管内皮生长因子(Vascular endothelial growth factor, VEGF)、血管内皮生长因子受体(Vascular endothelial growth factor receptor, VEGFR)、碱性成纤维细胞生长因子(Basic fibroblast growth

factor, bFGF)及微血管密度(MVD)值。由专人采集患者清晨空腹状态下的外周静脉血 5 mL,并用肝素抗凝处理,启动离心机以 2000 r/min 速率进行离心,抽吸上层血浆并将其放入 -20 ℃冰箱中封存,利用双抗体夹心 ELISA 试剂盒(由美国 R&D 公司生产)对上述指标剂量进行检测。③记录两组患者治疗期间不良反应的发生率。

1.4 统计学方法

采用 SPSS20.0 软件进行统计分析,正态分布的连续型资料以均数±标准差($\bar{x} \pm s$)作为统计描述,组间比较采取两独立样本 t 检验;离散型资料以率作为统计描述,采取 X^2 检验, $P<0.05$ 说明差异有统计学意义。

2 结果

2.1 两组患者临床有效率比较

研究组完全缓解 25 例,部分缓解 12 例,未缓解 5 例,有效率为 88.4%,对照组完全缓解 15 例,部分缓解 18 例,未缓解 10 例,有效率为 76.7%,差异有统计学意义($P<0.05$)。见表 2。

表 2 两组患者临床有效率比较(例)
Table 2 Comparison of clinical efficiency between two groups(cases)

Group	N	Complete remission	Partial remission	No remission	Efficiency[n(%)]
Study group	43	25	13	5	38(88.4 %)
Control group	43	15	18	10	33(76.7 %)
X^2	—	—	—	—	8.167
P	—	—	—	—	<0.05

2.2 两组患者治疗前后 VEGF、VEGFR、bFGF 及 MVD 值比较

治疗前,两组 VEGF、VEGFR、bFGF 及 MVD 无显著差异($P>0.05$);治疗后,研究组 VEGF、VEGFR、bFGF 及 MVD 均低于对照组,差异有统计学意义($P<0.05$)。见表 3。

2.3 两组治疗期间不良事件发生率比较

研究组出现骨髓抑制 26 例,恶心/呕吐 1 例,失眠 3 例,肝功能损害 2 例,肾功能损害 2 例,不良事件发生率为 79.1%(31/43),对照组出现骨髓抑制 25 例,恶心/呕吐 3 例,失眠 1 例,肝功能损害 3 例,肾功能损害 3 例,不良事件发生率为 81.4%(29/43),差异无统计学意义($P>0.05$)。见表 4。

表 3 两组患者治疗前后 VEGF、VEGFR、bFGF 及 MVD 值比较(n=43)

Table 3 Comparison of VEGF, VEGFR, bFGF and MVD before and after the treatment(n=43)

Items	Group	Before treatment	t	P	After treatment	t	P
VEGF	Study group	372.9± 19.4	0.973	>0.05	207.8± 9.6	9.468	<0.05
	Control group	378.1± 20.1			293.5± 16.8		
VEGFR	Study group	2384.8± 138.1	0.044	>0.05	1341.7± 106.8	12.751	<0.05
	Control group	2213.6± 130.5			1857.2± 113.7		
bFGF	Study group	2.6± 0.6	1.420	>0.05	2.0± 0.3	6.456	<0.05
	Control group	2.5± 0.5			2.4± 0.4		
MVD	Study group	21.5± 3.8	1.289	>0.05	8.4± 2.7	13.281	<0.05
	Control group	22.0± 3.9			15.7± 3.0		

表 4 两组患者治疗期间不良事件发生率比较

Table 4 Comparison of incidence of adverse events between the two groups

Group	N	Bone marrow suppression	Nausea / vomiting	Sleepiness	Liver function damage	Impairment of renal function	Incidence rate [n(%)]
Study group	43	26	1	3	2	2	34(79.1)
Control group	43	25	3	1	3	3	35(81.4)
X ²	—	—	—	—	—	—	13.297
P	—	—	—	—	—	—	<0.05

3 讨论

目前,对于血液系统恶性肿瘤患者,临床认为骨髓移植是最为有效的治疗手段,但骨髓来源极其有限,且移植费用昂贵,在应用和开展方面受到一定限制^[9]。部分血液病患者主要以化疗为主,辅以生物疗法、免疫治疗及放疗等方案,虽然对病情起到一定程度的遏制作用,但仍难以降低死亡率^[10]。有研究发现,新生血管大量增殖与急性白血病的病情进展密切相关^[11]。VEGF、VEGFR、bFGF 等促血管生长因子对血管形成具有正性调节作用,能够促进毛细血管生长和异常血细胞增殖。促血管生长因子含量一旦超出机体正常调控范围,将会影响白血病细胞生长、浸润及转移。因此,选择一种有效抗血管生长的治疗手段是目前研究的重点。

沙利度胺是一类谷氨酸衍生物,它具有较佳的免疫调节及抗血管生长效应,对淋巴瘤、多发性骨髓瘤及多种实体肿瘤均取得可观疗效^[12-14]。基于沙利度胺所具备的新生血管抑制潜能,有学者提出将该药应用于急性白血病治疗当中^[15]。本研究结果显示,研究组临床有效率高于对照组($P<0.05$),表明沙利度胺可协同常规化疗方案抗癌效果。我们考虑这主要与沙利度胺抗血管生长机制相关,分析两组治疗前后各项促血管生长因子水平后发现,两组在治疗前的各项促血管生长因子水平差异无统计学意义($P>0.05$);而治疗后,研究组 VEGF、VEGFR、bFGF 及 MVD 值均低于对照组($P<0.05$),这进一步证实沙利度胺具有抑制恶性血液病血管新生及生长的作用。

由于急性白血病患者骨髓造血功能被大量异常血细胞浸润、侵袭而影响其正常造血功能,导致血红蛋白、血小板减少,

使机体长期处于贫血及生理应激状态,这会激活机体血液代偿机制,诱发组织细胞分泌大量 VEGF 使新生血管生成^[16,17]。再加上化疗药物的应用,会进一步破坏机体正常血液细胞,亦会加强机体代偿机制,使 VEGF 分泌水平增大^[18]。而随着 VEGF 与受体 VEGFR 结合,将会刺激血管内皮细胞增殖,使血管生长,这不仅会进一步促进白血病细胞自身增殖,更是为癌细胞生长创造了有利的内在微环境,使其形成恶性循环^[19]。据文献指出,VEGF 与骨髓 MVD 呈正相关,这提示 VEGF 可借助自分泌和旁分泌途径使微血管数目增加,并促进白细胞大量增殖,这表明 VEGF 实际上是急性白血病治疗中需重点关注的主要调控因子,只有降低 VEGF 水平,方可减少异常白血病增殖,利于病情预后。而沙利度胺不仅能有效降低 VEGF 及 bFGF 等促血管生长因子的分泌水平,还能通过环氧化物酶途径降低微血管内皮细胞密度,进而达到抗肿瘤目的^[20-22]。

在两组不良反应发生率方面,差异无统计学意义($P>0.05$),其中研究组嗜睡发生 3 例,对照组 1 例,而嗜睡则能帮助恢复精力,提高患者化疗期间耐受性及治疗依从性。研究组发生恶心/呕吐为 1 例,对照组为 3 例,主要是沙利度胺本身具有中枢性止吐效果,能减轻化疗期间所产生的胃肠道反应。

综上所述,对于急性白血病患者而言,在常规化疗方案基础上联合应用沙利度胺,可减少促血管生长因子含量,且安全性佳,值得在临床上进一步推广。

参考文献(References)

- [1] Bersvendsen H, Kolstad A, Blystad AK, et al. Multimodal treatment with ALL-like chemotherapy, Auto-SCT and radiotherapy for lymphoblastic lymphoma[J]. Acta Oncol, 2014, 53(5): 680-687
- [2] Seif AE, Fisher BT, Li YM, et al. Patient and hospital factors

- associated with induction mortality in acute lymphoblastic leukemia [J]. *Pediatr Blood Cancer*, 2014, 61(5): 846-852
- [3] Cattaneo C, Antoniazzi F, Tumbarello M, et al. Relapsing bloodstream infections during treatment of acute leukemia[J]. *Ann Hematol*, 2014, 93(5): 785-790
- [4] Devitt KA, Lunde JH, Lewis MR. New onset pancytopenia in adults: a review of underlying pathologies and their associated clinical and laboratory findings[J]. *Leuk Lymphoma*, 2014, 55(5): 1099-1105
- [5] Gulia S, Dangi U, Biswas S, et al. Prevalence and patterns of cytomegalovirus DNAemia in adult patients with acute lymphoblastic leukemia on chemotherapy [J]. *Leuk Lymphoma*, 2014, 55 (5): 1209-1211
- [6] Nazha A, Ravandi F. Acute myeloid leukemia in the elderly: do we know who should be treated and how [J]. *Leuk Lymphoma*, 2014, 55 (5): 979-987
- [7] Olcay L, Hazirolan T, Yildirmak Y, et al. Biochemical, Radiologic, Ultrastructural, and Genetic Evaluation of Iron Overload in Acute Leukemia and Iron-chelation Therapy [J]. *J Pediatr Hematol Oncol*, 2014, 36(4): 281-292
- [8] Davis AS, Viera AJ, Mead MD. Leukemia: An Overview for Primary Care[J]. *Am Fam Physician*, 2014, 89(9): 731-738
- [9] Zhang Z. Blood standards disease diagnosis and efficacy (3 edition) [M]. Beijing: Science Press, 2007:103-121
- [10] Dulucq S, Laverdière C, Sinnett D, et al. Pharmacogenetic considerations for acute lymphoblastic leukemia therapies [J]. *Expert Opin Drug Metab Toxicol*, 2014, 10(5): 699-719
- [11] Salah EM, Abousamra NK, Azzam H. Clinical significance of minimal residual disease in young adults with standard-risk/Ph-negative precursor B-acute lymphoblastic leukemia: results of prospective study[J]. *Med Oncol*, 2014, 31(5): 938
- [12] Ibrahim L, Aladle D, Mansour A, et al. Expression and prognostic significance of livin/BIRC7 in childhood acute lymphoblastic leukemia[J]. *Med Oncol*, 2014, 31(5): 941
- [13] Huang BT, Zhao WH, Zeng QC, et al. Standard intensive chemotherapy is less effective and far more toxic than attenuated induction and post-induction regimen in elderly patients with acute myeloid leukemia[J]. *Med Oncol*, 2014, 31(5): 962
- [14] Nickel RS, Keller F, Bergsagel J, et al. Mitoxantrone as a substitute for daunorubicin during induction in newly diagnosed lymphoblastic leukemia and lymphoma [J]. *Pediatr Blood Cancer*, 2014, 61 (5): 810-814
- [15] Ozkan HA, Bal C, Gü lbas Z. Chemomobilization with high-dose etoposide and G-CSF results in effective and safe stem cell collection in heavily pretreated lymphoma patients: report from a single institution study and review[J]. *Eur J Haematol*, 2014, 92(5): 390-397
- [16] Kozłowski P, Åström M, Ahlberg L, et al. High relapse rate of T cell acute lymphoblastic leukemia in adults treated with Hyper-CVAD chemotherapy in Sweden[J]. *Eur J Haematol*, 2014, 92(5): 377-381
- [17] McAteer JP, Sanchez SE, Rutledge JC, et al. Isolated appendiceal typhlitis masquerading as perforated appendicitis in the setting of acute lymphoblastic leukemia[J]. *Pediatr Surg Int*, 2014, 30(5): 561-564
- [18] Gomes MZ, Jiang Ying, Mulanovich VE, et al. Effectiveness of Primary Anti-Aspergillus Prophylaxis during Remission Induction Chemotherapy of Acute Myeloid Leukemia [J]. *Antimicrob Agents Chemother*, 2014, 58(5): 2775-2780
- [19] Chen HY, Lu QY, Zhang YW, et al. Overexpression of SLC25A38 protein on acute lymphoblastic leukemia cells[J]. *Oncol Lett*, 2014, 7 (5): 1422-1426
- [20] Dong CH, Chen L. Second malignancies after breast cancer: The impact of adjuvant therapy[J]. *Mol Clin Oncol*, 2014, 2(3): 331-336
- [21] Liu WH, Chen YJ, Chien JH, et al. Amsacrine suppresses matrix metalloproteinase-2 (MMP-2)/MMP-9 expression in human leukemia cells[J]. *J Cell Physiol*, 2014, 229(5): 588-598
- [22] Zhao J, Zhang BP, Li SS, et al. Mangiferin increases Nrf2 protein stability by inhibiting its ubiquitination and degradation in human HL60 myeloid leukemia cells[J]. *Int J Mol Med*, 2014, 33(5): 1348-1354

(上接第 7051 页)

- [15] Snapir A, Talke P, Posti J, et al. Effects of nitric oxide synthase inhibition on dexmedetomidine-induced vasoconstriction in healthy human volunteers[J]. *Br J Anaesth*, 2009, 102(1): 38-46
- [16] Kleinbongard P, Schulz R, Rassaf T, et al. Red blood cells express a functional endothelial nitric oxide synthase [J]. *Blood*, 2006, 107(7): 2943-2951
- [17] Sundquist J, Blas SD, Hogan JE, et al. The alpha1-adrenergic receptor in human erythrocyte membranes mediates interaction in vitro of epinephrine and thyroid hormone at the membrane Ca2+-ATPase[J]. *Cell Signal*, 1992, 4(6): 795-799
- [18] 蒋心惠, 周岐新. 高效液相法测定硫酸特布他林与红细胞膜表面β2 肾上腺受体结合量[J]. *分析化学*, 2010, 38(3): 377-380
- Jiang Xin-hui, Zhou Qi-xin. Determination of terbutaline sulfate and its combination with β2 adrenergic receptor in erythrocyte membrane by high performance liquid chromatography [J]. *Chinese Journal of Analytical Chemistry*, 2010, 38(3): 377-380
- [19] 张英, 唐显玲. 不同麻醉方式对血液流变学的影响[J]. *国际麻醉学与复苏杂志*, 2010, 31(6): 546-549
- Zhang Ying, Tang Xian-ling. The affect of different anesthesia methods on hemorheology[J]. *J Anesth Resus*, 2010, 31(6): 546-549
- [20] 宋英晖, 韩曼宇. 红细胞变形性与疾病关系研究的近况[J]. *微循环学杂志*, 1998, 8(4): 22-23
- Song Ying-hui, Han Man-yu. Recent studies of the relationships between erythrocyte deformability and diseases[J]. *Chinese Journal of Microcirculation*, 1998, 8(4): 22-23