

p16基因缺失在成人Ph染色体阳性急性淋巴细胞白血病中的临床意义

何柏林 许娜 李玉玲 潘成云 曹睿 廖立斌 阴常欣
蓝扬清 陆紫媛 黄继贤 周红升 刘启发 刘晓力

【摘要】 目的 探讨p16基因缺失在成人Ph染色体阳性急性淋巴细胞白血病(Ph⁺ ALL)中的临床意义。方法 回顾性分析80例Ph⁺ ALL伴p16基因缺失患者的临床特征、免疫表型、细胞遗传学、分子生物学改变及其预后。结果 31.3% Ph⁺ ALL患者合并p16基因缺失;p16基因缺失组与非缺失组相比,初诊时高白细胞计数(WBC \geq 30 \times 10⁹/L)更常见,高表达CD20,更易出现附加染色体异常,其中以累及7、8、19号染色体以及der(22)较为常见;两组诱导缓解率比较差异无统计学意义($P=0.033$),p16基因缺失组患者治疗3个疗程后获BCR-ABL融合基因主要分子学反应(MMR)率和完全分子学反应(CMR)率均明显低于非缺失组(P 值分别为0.034和0.036),且复发率明显高于非缺失组($P=0.033$);p16基因缺失组使用伊马替尼联合化疗者和使用达沙替尼联合化疗者的MMR、CMR率及复发率差异均无统计学意义(P 值均 >0.05);p16基因缺失组患者3年总体生存(OS)率及无病生存(DFS)率分别为37.1%和12.4%,显著低于非缺失组的54.1%和45.9%(P 值分别为0.037和0.026);25例p16基因缺失患者中14例行异基因造血干细胞移植(allo-HSCT),其中位OS时间为21个月,明显长于非移植组患者的12个月($P=0.030$)。结论 成人Ph⁺ ALL伴p16基因缺失患者预后相对较差,二代酪氨酸激酶抑制剂不能明显改善其疗效,但allo-HSCT能够改善部分患者的生存,明确p16基因缺失状态对于评估预后和指导临床治疗有重要意义。

【关键词】 p16基因缺失; 费城染色体; 白血病,淋巴细胞,急性; 酪氨酸激酶抑制剂; 造血干细胞移植

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Clinical analysis of adult Philadelphia chromosome-positive acute lymphoblastic leukemia with p16 gene deletion He Bolin, Xu Na, Li Yuling, Pan Chengyun, Cao Rui, Liao Libin, Yin Changxin, Lan Yangqing, Lu Ziyuan, Huang Jixian, Zhou Hongsheng, Liu Qifa, Liu Xiaoli. Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China
Corresponding author: Liu Xiaoli, Email: lx12405@126.com

【Abstract】 Objective To investigate the clinical implications of p16 gene deletion in adult Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph⁺ ALL). **Methods** Retrospective analysis of clinical, immunophenotypic, cytogenetics, molecular characteristics and prognosis of 80 newly diagnosed Ph⁺ ALL patients with p16 deletion. **Results** Of 80 adult Ph⁺ ALL, the prevalence of p16 gene deletion was 31.3%. p16 gene deletion carriers frequently accompanied with high WBC counts (WBC \geq 30 \times 10⁹/L) and CD20 expression. The incidence of complex chromosome abnormality in p16 gene deletion group was higher than that in non-deletion group, with alternations in chromosome 7, 8, 19 and der(22) more frequently observed. There was no difference occurred between patients with or without p16 gene deletion in complete remission (CR) rate following induction chemotherapy combined with tyrosine kinase inhibitors (TKIs). However, after three cycles of chemotherapy, the MMR and CMR rate in the p16 gene deletion group was lower than patients with wild-type p16 gene ($P=0.034$, $P=0.036$). The p16 gene deletion patients showed no significant differences in MMR, CMR and relapse rate between Imatinib or Dasatinib plus chemotherapy ($P>0.05$). Deletion of p16 gene was significantly associated with poor

outcomes including worse overall survival (OS) (37.1% vs 54.1%, $P=0.037$), lower disease free-survival (DFS) (12.4% vs 45.9%, $P=0.026$), and increased cumulative incidence of relapse ($P=0.033$). Among the 25 patients with p16 deletion, 14 underwent allo-HSCT and the median survival was 21 months, better than that of patients received chemotherapy alone (12 months) ($P=0.030$). **Conclusion** This study indicated that deletion of p16 was associated with poor prognosis in adult Ph⁺ ALL, and the utility of second-generation TKI (Dasatinib) does not necessarily have an edge on efficacy over Imatinib, but allo-HSCT has the potential of elongating life expectancy. It is an important significance to define the status of p16 in Ph⁺ ALL for predicting prognosis and guiding therapy decision-making.

【Key words】 p16 gene deletion; Philadelphia chromosome; Leukemia, lymphoid, acute; Tyrosine kinase inhibitor; Hematopoietic stem cell transplantation

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Ph染色体是急性淋巴细胞白血病(ALL)常见的细胞遗传学异常,酪氨酸激酶抑制剂(TKI)联合化疗及异基因造血干细胞移植(allo-HSCT)可显著改善Ph⁺ALL的预后,但是仍有部分患者出现耐药、复发甚至疾病进展^[1]。TKI耐药仍是目前Ph⁺ALL治疗的一大难点,因此,探讨TKI耐药机制以及寻找新的预后标志对于该部分患者显得尤其重要。染色体9p21的异常在多种肿瘤的发生发展中起重要作用^[2]。目前已经发现在9p21区域有CDKN2A(p16)和CDKN2B(p15)两个重要的抑癌基因,它们分别编码p16(INK4a)/p14(ARF)和p15(INK4b)周期蛋白,构成了一个重要的抑癌基因簇^[3]。在ALL中,18.2%~45.0%的患者可以检测到p16基因缺失,我们前期研究及目前文献报道p16基因缺失可能是ALL预后不良的独立危险因素^[4-5]。本研究中我们应用FISH技术检测80例初诊Ph⁺ALL患者p16基因缺失情况,并进一步分析该基因缺失与Ph⁺ALL患者临床特征、疗效及预后关系。

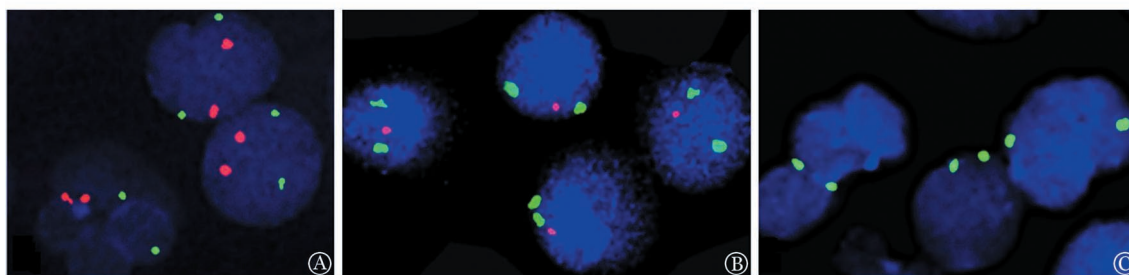
病例与方法

1. 病例资料:对2010年1月至2015年4月就诊于我院血液科的80例初诊Ph⁺ALL患者的临床资料进行回顾性分析,所有患者均根据临床表现、骨髓

细胞形态学、免疫分型、细胞遗传学及分子生物学结果进行诊断,符合WHO(2008)急性白血病诊断标准。骨髓细胞核型分析采用常规G显带法。骨髓细胞免疫表型分析采用流式细胞术检测淋系和髓系抗原。BCR-ABL mRNA检测采用常规实时荧光定量PCR(RQ-PCR)方法,以ABL作为内参基因,BCR-ABL mRNA水平以BCR-ABL/ABL基因转录本拷贝数×100%表示,敏感度为MR4.5(BCR-ABL^{IS}=0.0032%)^[6]。

2. FISH法检测p16基因缺失:针对p16基因缺失的预包被式探针诊断系统购于英国Cytocell公司,按设计组合标记固定于一张检测玻片,按试剂盒说明书进行操作。探针组包括:覆盖9p21区域101 kb的红色探针,9号染色体质控探针(D923, 9q12上的异染色质块,绿色)。正常细胞的荧光原位杂交信号为2红2绿,1红2绿表明p16基因从1条染色体中缺失,即杂合性缺失,0红2绿为纯合性缺失(图1)。杂合性缺失与纯合性缺失均定义为缺失。根据ISCN(2005)标准分析检测结果,每份间期核标本计数200个细胞^[7]。

3. 治疗方案:所有Ph⁺ALL患者均首先予VILP(长春新碱、去甲氧柔红霉素、左旋门冬酰胺酶、泼尼松)或VDLP(长春新碱、柔红霉素、左旋门冬酰胺



A: 正常细胞; B: 杂合性缺失; C: 纯合性缺失

图1 荧光原位杂交分析p16基因缺失

酶、泼尼松)方案进行诱导化疗,明确诊断后尽早联合TKI药物治疗(伊马替尼400 mg 每日1次或达沙替尼100 mg 每日1次)。诱导缓解后予Hyper CVAD-A(环磷酰胺、长春新碱、阿霉素、地塞米松)方案和Hyper CVAD-B(大剂量甲氨蝶呤和阿糖胞苷)方案交替巩固治疗。其中54例患者在巩固化疗2~5个疗程后进行allo-HSCT。对所有患者均进行腰椎穿刺并鞘内注射药物(阿糖胞苷+甲氨蝶呤+地塞米松)预防中枢神经系统白血病。

4. 疗效评估:首疗程诱导治疗结束后行骨髓细胞形态学检查,评价血液学缓解情况;3个疗程后疗效评价主要根据细胞分子学反应。完全缓解(CR)定义为化疗后患者骨髓中原始细胞 ≤ 0.050 ,外周血中性粒细胞绝对计数 $\geq 1.5 \times 10^9/L$, $PLT \geq 100 \times 10^9/L$,白细胞分类中无白血病细胞,无髓外白血病。主要分子学反应(MMR)定义为BCR-ABL mRNA较治疗前下降至少3个对数级($BCR-ABL/ABL \leq 0.1\%$)。完全分子学反应(CMR)定义为BCR-ABL mRNA拷贝数低于检测极限水平($BCR-ABL/ABL \leq 0.0032\%$)^[6,8]。复发定义为获得CR患者骨髓中原始细胞 ≥ 0.050 或者发生髓外侵犯。总生存(OS)时间指从诊断起至患者死亡(包括任何原因)或末次随访日止。无病生存(DFS)时间定义为自CR至白血病复发或在CR期间死亡或末次随访日。随访截止日期为2016年5月4日。

5. 统计学处理:应用SPSS 20.0统计学软件进行分析,样本均数的比较采用t检验,率的比较采用卡方检验,生存率的比较采用Log-rank检验,采用Kaplan-Meier法绘制生存曲线。 $P < 0.05$ 为差异有统计学意义。

结 果

1. 伴p16基因缺失Ph⁺ALL患者临床及实验室特征:本组80例成人Ph⁺ALL患者中位年龄33.5(18~61)岁。25例(31.3%)患者检出p16基因缺失,其中1例为杂合缺失,24例为纯合缺失。p16基因缺失与未缺失组相比,性别、年龄、中位WBC、骨髓中原始细胞比例、肝脾肿大及髓外浸润情况等差异均无统计学意义(P 值均 > 0.05)。p16基因缺失患者初发高白细胞($WBC \geq 30 \times 10^9/L$)比非缺失组更常见($P = 0.042$)(表1)。在p16基因缺失组中,除2例核型分析失败的患者,余23例中18例(78.3%)初诊核型分析存在Ph染色体伴附加染色体异常,发生率较非缺失组高($P = 0.035$),其中以累及7号染色体(4例,3例-7,1例7q-)、8号染色体(4例,3例易位)、19号染色体(3例,2例-19,1例+19)和der(22)(4例)更为常见。此外,本组病例中发现的Ph染色体变异型易位有t(8;9;22)(q21;q34;q11)、t(4;9;22)(q21;q34;q11)、t(9;9;22)(q22;p24;q11)。

2. 伴p16基因缺失Ph⁺ALL免疫表型分析:对80

表1 伴p16基因缺失Ph⁺急性淋巴细胞白血病患者临床及实验室特征

特征	缺失阳性组 (25例)	缺失阴性组 (55例)	检验值	P值
中位年龄[岁, M(范围)]	34(18~60)	28(18~61)	-1.610*	0.111
性别(例,男/女)	17/8	34/21	0.284	0.594
WBC[$\times 10^9/L$, M(范围)]	49.72(1.70~255.96)	39.00(1.78~808.00)	0.539*	0.592
WBC $\geq 30 \times 10^9/L$ [例(%)]	20(80.0)	31(56.4)	4.155	0.042
骨髓原始细胞[M(范围)]	0.838(0.400~0.995)	0.816(0.260~0.995)	-0.549*	0.584
肝脾肿大[例(%)]	10(40.0)	14(25.4)	1.732	0.188
髓外浸润[例(%)]	4(16.0)	12(21.8)	0.364	0.546
CD20阳性[例(%)]	14(56.0)	17(30.9)	4.558	0.033
细胞遗传学异常[例(%)]			4.461	0.035
单纯Ph染色体	5(21.7)	23(47.9)		
Ph伴附加染色体	18(78.3)	25(52.1)		
首疗程完全缓解[例(%)]	21(84.0)	51(92.7)	1.455	0.228
获主要分子学反应[例(%)]	4(16.0)	22(40.0)	4.513	0.034
获完全分子学反应[例(%)]	2(8.0)	16(29.1)	4.384	0.036
造血干细胞移植[例(%)]	14(56.0)	40(72.7)	2.192	0.139
复发[例(%)]	15(60.0)	19(34.5)	4.557	0.033

注:检验值中*为t值,余均为 χ^2 值

例成人Ph⁺ALL患者骨髓细胞进行免疫表型分析,CD抗原表达>20%为阳性。p16基因缺失与未缺失组相比,除CD20外,两组间CD45、CD13、CD14、CD15、CD117、CD33、CD34、CD38、HLA-DR、CD10、CD19、CD22、CD2、CD3、CD7、CD11b、CD56等表达差异均无统计学意义(P 值均>0.05),p16基因缺失患者多合并CD20表达($P=0.033$)。

3. 伴p16基因缺失Ph⁺ALL疗效分析:p16基因缺失组使用VDLP诱导方案14例,VILP诱导方案11例,非缺失组分别为37例和18例,两组差异无统计学意义($P=0.331$)。p16基因缺失组与非缺失组患者化疗联合伊马替尼治疗分别为13例和29例,联合达沙替尼治疗分别为12例和26例,两组差异无统计学意义($P=0.952$)。p16基因缺失组与非缺失组相比,首疗程诱导治疗CR率差异无统计学意义(84.0%对92.7%, $P=0.249$)。p16基因缺失组治疗3个疗程后MMR率为16.0%,CMR率为8.0%,显著低于非缺失组的40.0%和29.1%(P 值分别为0.034和0.036)(表1)。两组患者BCR-ABL转录本均以P190为主,p16基因缺失组中P190阳性19例,p210阳性6例,非缺失组分别为40例和15例,差异无统计学意义($P=0.758$)。p16基因缺失组中15例(60.0%)患者出现复发(血液学或中枢神经系统复发),复发率明显高于非缺失组(34.5%, $P=0.033$)。p16基因缺失组患者中化疗联合伊马替尼治疗13例,联合达沙替尼治疗12例,两者的MMR(15.4%对16.7%, $P=0.930$)、CMR率(7.7%对8.3%, $P=0.953$)及复发率(61.5%对58.3%, $P=0.870$)差异均无统计学意义。

4. 伴p16基因缺失Ph⁺ALL患者生存分析:80例成人Ph⁺ALL患者中54例在巩固化疗2~5个疗程后进行allo-HSCT,其中p16基因缺失组14例,非缺失组40例,截至末次随访,80例患者中位随访时间为19.5(2~79)个月。p16基因缺失组和非缺失组患者中位生存时间分别为18和47个月($P=0.037$)。p16基因缺失组患者3年OS率及DFS率分别为37.1%、12.4%,而非缺失组分别为54.1%、45.9%,差异均有统计学意义(P 值分别为0.026和0.030)(图2、3)。p16基因缺失患者中移植组中位生存时间为21个月,非移植组为12个月($P=0.030$)(图4)。

讨 论

2014年NCCN指南中将ALL分为高危组和标

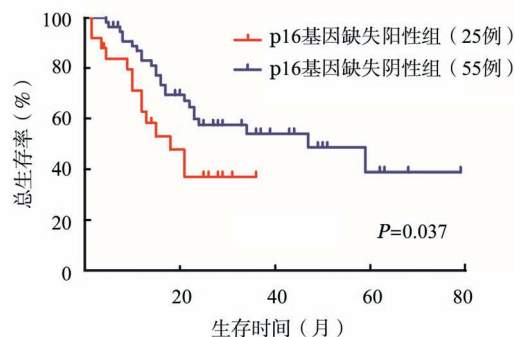


图2 p16基因缺失阳性和阴性Ph⁺急性淋巴细胞白血病患者总生存曲线

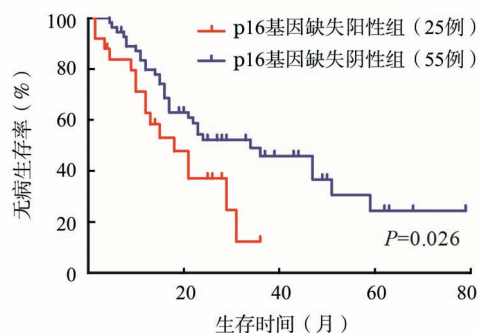


图3 p16基因缺失阳性和阴性Ph⁺急性淋巴细胞白血病患者无病生存曲线

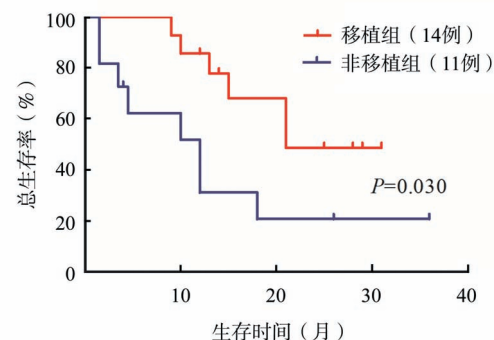


图4 异基因造血干细胞移植治疗对Ph⁺急性淋巴细胞白血病伴p16基因缺失患者总生存的影响

危组,定义高危组ALL的危险因素有:①Ph阳性或BCR-ABL基因阳性;②t(v;11q23)或MLL基因重排;③诊断时WBC $\geq 30 \times 10^9/L$ (B-ALL), $\geq 100 \times 10^9/L$ (T-ALL);④低二倍体(染色体数<44条)。标危组ALL则不具有上述任何危险因素之一^[7]。近年基于疾病危险度的分层诊断和TKI的应用及allo-HSCT方案的优化显著改善了Ph⁺ALL患者的预后,但是仍有部分患者出现复发,难以从目前的诊疗中获益,强烈提示此类疾病需要再分层。我们曾报道p16基因缺失儿童和成人B-ALL患者预后相对较

差^[4,9],且国外有报道,p16基因缺失是Ph⁺ALL除BCR-ABL融合基因外最常见的基因突变之一,其检出率为29.2%~64.0%^[10-11]。Mullighan等^[12]还发现Ph⁺ALL和慢性髓性白血病ALL变患者伴p16基因缺失的细胞遗传学改变可能是影响伊马替尼疗效的原因之一。

本研究结果显示,p16基因缺失在成人Ph⁺ALL中的发生率为31.3%,与文献^[9-11]报道相符。我们发现,p16基因缺失组患者具有初诊高白细胞(WBC \geq 30 \times 10⁹/L)、CD20阳性率高以及伴随附加染色体异常更常见的特点。目前CD20阳性对Ph⁺ALL预后的影响仍然存在争议^[13-14],但是多数研究认为CD20阳性与ALL复发率增高、CR持续时间缩短及生存率降低密切相关^[15-16],利妥昔单抗联合标准化疗能有效延长60岁以下CD20阳性ALL患者的OS时间^[16]。基于上述研究及我们发现p16基因缺失组患者更容易高表达CD20、预后差、复发率高等特点,我们研究组推测利妥昔单抗有可能改善p16基因缺失患者的预后,但目前无相关报道,仍需进一步研究证实。本研究结果还显示,p16基因缺失组患者更易伴随附加染色体异常,可能主要因为p16基因可以通过抑制CDK4/6-cyclinD复合物激酶活性,使Rb呈持续高磷酸的活化状态,从而抑制细胞由G₁期进入到S期,导致细胞周期停滞^[3,17]。本研究中p16基因缺失患者出现附加染色体异常以累及7、8、19号染色体以及der(22)更为常见,Wetzler等^[18]的研究亦表明Ph⁺ALL患者伴7号染色体异常和der(22)异常往往提示预后不良。

我们在研究中发现,Ph⁺ALL伴p16基因缺失患者治疗效果差,复发率高,3年OS及DFS率明显低于非缺失患者,与国外大部分报道一致^[19-21]。p16基因缺失组患者中化疗联合伊马替尼治疗13例,联合达沙替尼治疗12例,两者的MMR、CMR、复发率差异无统计学意义。早有报道伊马替尼治疗p16基因缺失Ph⁺ALL的效果不佳^[12],Williams等^[22-23]通过用BCR-ABL基因转染p16基因缺失的小鼠骨髓细胞发现,该小鼠对伊马替尼治疗敏感性差,并且证实p16基因缺失通过细胞因子IL-7依赖形式诱导细胞对伊马替尼耐药。目前越来越多的报道显示,二代TKI(达沙替尼)联合化疗可明显改善Ph⁺ALL疗效及预后^[24-25],国外多中心研究发现仅接受达沙替尼联合化疗治疗的Ph⁺ALL患者可获得持续缓解和长期生存(中位OS时间为55个月)^[24]。而本研究发现,Ph⁺ALL伴p16基因缺失患者应用二代TKI如达

沙替尼并不能获得更深层次的MMR以及减少复发,也许与本研究病例数少有关。目前尚缺少针对p16基因缺失的靶向治疗药物,但我们的研究结果显示,allo-HSCT能够改善伴p16基因缺失患者的预后,为该部分患者的治疗选择提供了数据。

综上所述,成人Ph⁺ALL伴p16基因缺失的患者预后相对较差,使用二代TKI不能明显改善该部分患者的疗效,但allo-HSCT能够延长患者的生存时间,因此,明确p16基因缺失状态对于Ph⁺ALL预后评估和指导临床治疗具有重要意义。

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