·论著·

异基因造血干细胞移植治疗原发性血小板增多症转化的急性髓系白血病三例报告并文献复习

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【摘要】 **目的** 探讨原发性血小板增多症(ET)转化急性髓系白血病(AML)的病情变化特点及异基因造血干细胞移植(allo-HSCT)的治疗价值。**方法** 回顾性分析3例ET转AML患者的临床特征、实验室检查结果及诊治经过,复习相关文献。**结果** 例1,男,44岁,初诊ET时PLT 500×10⁹/L,3年后疾病转变为骨髓增生异常综合征时WT1基因由初诊时77拷贝/10 000 ABL拷贝升至13 171拷贝/10 000 ABL拷贝,染色体核型发生异常改变,在地西他滨治疗过程中快速进展为AML。例2,男,58岁,诊断ET时PLT 2 100×10⁹/L,9年后疾病进展为AML,WT1基因由初诊时130拷贝/10 000 ABL拷贝升至3 222拷贝/10 000 ABL拷贝,在化疗期间短期内复发。例3,男,60岁,初诊ET时PLT 900×10⁹/L,5年后疾病转化为AML,WT1基因由初诊时56拷贝/10 000 ABL拷贝升至3 696拷贝/10 000 ABL拷贝,化疗期间出现中枢神经系统侵犯。例1移植前未缓解,例2缓解后短期内复发,例3出现髓外侵犯。3例患者均顺利完成allo-HSCT,移植后骨髓缓解,染色体核型正常,例3中枢神经系统病灶消失,JAK2基因突变均转阴,WT1基因表达均<200拷贝/10 000 ABL拷贝,未发生严重并发症。**结论** ET转化的AML病情凶险,allo-HSCT是目前唯一可能治愈此疾病的方法。

【关键词】 血小板增多,原发性; 白血病,髓样,急性; 造血干细胞移植

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Allogeneic hematopoietic stem cell transplantation for the treatment of acute myeloid leukemia with primary thrombocytosis: three cases report and literatures review *Zong Xiangping, Tang Lin, Cen Jiannong, Chen Suning, Sun Aining, Wu Depei. Jiangsu Institute of Hematology, the First Affiliated Hospital of Soochow University, Suzhou 215006, China*

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【**Abstract**】 **Objective** To investigate the characteristics of the essential thrombocythemia (ET) cases transformed to the acute myeloid leukemia (AML) and the role of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the treatment of this disease. **Methods** The clinical and laboratory characteristics of 3 ET cases before and after transformation and after allo-HSCT were retrospectively analyzed, meanwhile the related literatures were reviewed and discussed. **Results** Case 1 was a male patient of 44 years old, whose PLT was 500×10⁹/L when firstly diagnosed ET. After 3 years the disease progressed into myelodysplastic syndrome (MDS) while WT1 expression increased from 77 (first visit) to 13 171 copies/10 000 ABL copies, at the same time chromosome changed dramatically. During the period of decitabine treatment the disease processed into AML. Case 2 was a male of 58 years old whose PLT was 2 100×10⁹/L when firstly diagnosed ET. The disease progressed to AML after 9 years, whose WT1 expression increased from 130 (first visit) to 3 222 copies/10 000 ABL copies, and he relapsed shortly after intensive chemotherapy. Case 3 was a male of 60 years old whose PLT was 900×10⁹/L when firstly diagnosed ET. The disease progressed to AML after 5 years, whose WT1 increased from 56 (first visit) to

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3 696 copies/10 000 ABL copies. Moreover leukemia spread to central nervous system (CNS) during chemotherapy. Before allo-HSCT, cases 1 did not achieve remission; case 2 relapsed after a short time of remission and case 3 transferred to CNS leukemia. All of the 3 cases underwent allo-HSCT successfully, and they all achieved completely remission, whose chromosome and gene mutation recovered negative. At the same time, CNS leukemia of case 3 disappeared. The median WT1 decreased to 50 copies/10 000 ABL copies. There was no severe complication during the median time of 5 months after allo- HSCT. **Conclusions** The patients transformed to AML had poor prognosis, allo-HSCT was the only method that can cure the disease now.

【Key words】 Thrombocythemia, essential; Leukemia, myeloid, acute; Hematopoietic stem cell transplantation

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原发性血小板增多症(ET)是一种造血干细胞克隆性疾病,常伴有JAK2V617F基因突变。ET临床上主要表现为出血和血栓,但也可以进展为骨髓纤维化(MF)或急性髓系白血病(AML)。ET患者的AML转化率为0.5%~3.0%[1-2],进展至AML后病情凶险,普通治疗方法效果差,且对化疗不敏感,生存时间短。异基因造血干细胞移植(allo-HSCT)是目前唯一可能治愈的手段[3-4]。近年来,我们采用allo-HSCT治疗3例ET转化的AML患者,报告如下。

病例资料

例1,男,44岁,2013年体检发现血小板增多。血常规:WBC 5.54×10⁹/L,HGB 136 g/L,PLT 500×10⁹/L;骨髓象:增生活跃,粒红比例正常,巨核系增多;骨髓活检提示造血组织增生活跃,巨核细胞数增多;染色体核型正常;WT1基因77拷贝/10 000 ABL拷贝(正常参考值<200拷贝/10 000 ABL拷贝);JAK2V617F突变阳性。按照文献[5]标准诊断为ET。予以肠溶阿司匹林治疗,治疗期间血小板水平无明显波动。2016年1月血小板计数升高至655×10⁹/L,骨髓原幼细胞占0.090;染色体核型为46, XY, t(2; 11)(p23; q25)[6]/46, idem, del(5)(q13q33)[4];荧光原位杂交(FISH):5q31缺失阳性(82%),余阴性;免疫分型:幼稚细胞群占8.8%,CD34、HLA-DR、CD13、CD33、CD117阳性(髓系表达);WT1基因13 171拷贝/10 000 ABL拷贝。予以地西他滨50 mg/d×5 d治疗1个疗程后骨髓原幼细胞比例升至0.265,微小残留病(MRD)33.8%,染色体核型为46, XY, t(2; 11)(p23; q25)[5]/46, XY[5],提示疾病已进展为AML,后行挽救性女供父allo-HSCT[预处理方案:白消安+环磷酰胺;回输单个核细胞(MNC)8.86×10⁸/kg,CD34⁺细胞3.84×10⁶/kg]。+11 d粒系造血重建,+14 d巨核系造血重建。+30 d骨髓完全缓解,染色体核型:46,XX[10],WT1基因68拷贝/10 000 ABL拷贝,JAK2V617F突变阴性,短串联重复序列(STR)分析结果为90%。随访至移植后8个月,无明显移植物抗宿主病(GVHD)表现。

例2,男,58岁,2006年发现血小板增多,血常规:WBC 11.3×10⁹/L,HGB 123 g/L,PLT 2 100×10⁹/L,骨髓象:巨核细胞增多,染色体核型正常;骨髓活检:符合ET表现;WT1基因130拷贝/10 000ABL拷贝,JAK2V617F突变阳性。按照文献[5]标准诊断为ET。予皮下间断使用干扰素,维持PLT 600×10⁹/L。2015年10月因头痛伴反复发热查血常规:WBC 70.56×10⁹/L、HGB 62 g/L、PLT 96×10⁹/L,骨髓原幼细胞占0.950,染色体核型分析未见分裂象,免疫分型CD13、CD33、CD117强阳性(髓系表达),WT1基因3 222拷贝/10 000 ABL拷贝。诊断:ET转AML。予水化、碱化、白细胞去除术,IAC方案(去甲氧柔红霉素+阿糖胞苷+克拉曲宾)化疗未缓解,继以地西他滨+HAAG预激方案(三尖杉酯碱+阿糖胞苷+多柔比星+G-CSF)联合JAK2抑制剂芦可替尼治疗后骨髓完全缓解,以地西他滨+中大剂量阿糖胞苷继续治疗3次后行子供父微移植。末次微移植后短时间内复发(WBC 90.05×10⁹/L,HGB 81 g/L,PLT 335×10⁹/L,骨髓原幼细胞比例0.510),后行挽救性子供父单倍体移植[预处理方案:全身照射(TBI)联合氟达拉滨+环磷酰胺;回输MNC 10.03×10⁸/kg,CD34⁺细胞9.5×10⁶/kg]。+14 d粒系重建,+12 d巨核系重建。+30 d骨髓完全缓解,染色体核型:46,XY[10],WT1基因43拷贝/10 000 ABL拷贝,JAK2V617F突变阴性,STR 95%。随访至移

植后5个月，无明显GVHD表现。

例3，男，60岁，2011年体检时发现血小板计数偏高而就诊。血常规：WBC 8.65×10⁹/L，HGB 140 g/L，PLT 900×10⁹/L，骨髓形态及活检符合ET，染色体核型正常，WT1基因56拷贝/10 000ABL拷贝，JAK2V617F突变阳性，按照文献[5]标准诊断为ET。先后使用干扰素、羟基脲，血小板计数控制在正常范围。2016年2月血常规：WBC 6.6×10⁹/L，HGB 124 g/L，PLT 80×10⁹/L；外周血幼稚细胞占0.260；骨髓原始粒细胞占0.670；染色体核型：47，XY，+1，der(1；7)(q10；p10)，+8，add(14)(q32)[20]；免疫分型HLA-DR、CD4、CD13、CD33、CD34、CD38、CD117、CD112阳性(髓系表达)；WT1基因3 696拷贝/10 000ABL拷贝。诊断：ET转AML。予以地西他滨+IAG方案(去甲氧柔红霉素+阿糖胞苷+G-CSF)诱导治疗后缓解，巩固1个疗程发生中枢神经系统白血病，予以化疗联合定期鞘内注射(阿糖胞苷+甲氨蝶呤+地塞米松)，脑脊液幼稚细胞转阴、颅内病灶明显缩小后行非亲缘allo-HSCT(预处理方案：地西他滨+TBI+环磷酰胺；回输MNC 11.7×10⁸/kg，CD34⁺细胞3.39×10⁶/kg)。+12 d粒系重建，+15 d巨核系重建。+30 d骨髓完全缓解，染色体核型：46，XY[10]，WT1基因50拷贝/10 000 ABL拷贝，JAK2V617F突变转阴，STR 92%，头颅病灶消失。随访至移植后3个月，无明显GVHD表现。

讨论及文献复习

ET转化AML后支持治疗及细胞毒药物化疗效果均非常有限，生存期很短，短期内容易对各种化疗药物产生耐药[6]。Kennedy等[7]报道只有44%的Ph阴性骨髓增殖性肿瘤转化AML的患者在造血干细胞移植前能获得缓解。造血干细胞移植治疗PV/ET转化的AML或MF患者的3年总生存(OS)率为39%～67%[3-4,8]。

本研究中例2及例3均为高龄，疾病凶险，化疗期间短时间内复发，对化疗药物治疗效果不佳，与文献[6]报道相符，且例3并发中枢神经系统白血病，如不进行allo-HSCT，生存时间极短。3例患者移植前均未获得缓解，予清髓性预处理，造血重建顺利，均达到分子学缓解。移植前状态是移植后能否获得长期生存的关键因素[9]。allo-HSCT可使20%以上的未缓解患者获得长期生存[9-10]。本组3例患者移植前均未缓解，虽然移植后达到分子学缓解，延长了生存时间，但后期复发率仍然很高，需继续关注。研究认为ET转变越早，移植带来的收益越多，充分提示了移植时机的选择的重要性[4,11-12]。因此，虽然ET经常表现为一个惰性慢性疾病，但如果有高危因素(如反复发生血栓事件或疾病本身难以控制)，需尽早行allo-HSCT[4]。WT1基因在本组3例患者的病程中显示了充分的提示及判断病情的作用，是否可作为评估病情进展及提早干预的依据有待于更多数据的收集。

Lussana等[13]报告了allo-HSCT治疗250例PV/ET转变为MF或AML患者的结果，清髓性和减低强度预处理方案两组患者3年OS率差异无统计学意义(56%对55%，$P=0.231$)，后者复发率稍高；而≥55岁患者3年非复发死亡率较高(35%对20%，$P=0.032$)；无关供者组死亡率高于全相合供者组(34%对18%，$P=0.034$)；转变为AML组死亡率高于转化为MF组(29%对27%，$P=0.045$)；死亡原因主要为移植后6个月内AML组感染、GVHD等事件。GVHD及复发仍是移植后需面对的问题，需要有更好的治疗方法。目前尚无allo-HSCT治疗ET转化AML患者的文献报道。

JAK2抑制剂芦可替尼是一种新的分子靶向药物，造血干细胞移植前后均有效，可以缩小脾脏、改善患者全身症状[14]。allo-HSCT联合分子靶向药物可能会降低移植风险，同时降低复发率及非复发死亡率。

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