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综述

重型地中海贫血的移植进展

黄楚雯 综述 江华 审校

(广州市妇女儿童医疗中心血液肿瘤科, 广东 广州 510623)

[摘要] 地中海贫血是因调节血红蛋白的基因突变导致珠蛋白链形成障碍的遗传性血液疾病。目前异基因造血干细胞移植是公认的唯一治愈手段, 其经历了预处理方案的演进, 供体及移植来源的对比选择等阶段, 现生存情况已得到提高。该文回顾了地中海贫血移植的发展过程及研究进展, 以期给临床提供更合适的治疗选择决策。
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[关键词] 地中海贫血; 造血干细胞移植; 儿童

Research advances in transplantation for thalassemia major

HUANG Chu-Wen, JIANG Hua. Department of Hematology and Oncology, Guangzhou Women and Children's Medical Center, Guangzhou 510623, China (Email: jiang_hua18@sina.com)

Abstract: Thalassemia is an inherited blood disorder caused by disordered globin chain synthesis due to mutations in the regulatory genes for hemoglobin. At present, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is recognized as the only curative method for treatment. Through the revolution of pretransplantation regimens and selection of donor and source of stem cells, patients' survival has been greatly improved. This article reviews the development of transplantation for thalassemia and related research advances, in order to provide suitable treatment options for clinical application.
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Key words: Thalassemia; Hematopoietic stem cell transplantation; Child

地中海贫血是常见的珠蛋白链组成缺陷相关的基因疾病。治疗方案有规律输血及去铁治疗、诱导胎儿蛋白形成、造血干细胞移植(hematopoietic stem cell transplantation, HSCT)和基因治疗^[1]。本文对重型地中海贫血(thalassemia major, TM)的HSCT进展进行综述。

1 地中海贫血的HSCT

1.1 预处理方案的演变

20世纪80年代, Pesaro中心移植了1000例以人类白细胞抗原(human leukocyte antigen, HLA)全相合同胞供体(matched sibling donor, MSD)TM患者, 20年无地中海贫血生存(thalassemia-free survival, TFS)率为73%^[2], 同时提出患者危险

分度(Pesaro分度), 以下3个危险因素: 肝脏体查位于肋下2cm、肝纤维化、不充分去铁, 依据包涵危险因素的数量分为I级: 无危险因素; II级: 1~2个危险因素; III级: 3个危险因素均有。Lucarelli等^[3]首次提出基于环磷酰胺(Cy)200mg/kg+白消安(Bu)14~16mg/kg清髓预处理方案治疗30例TM患者, 2年总体生存(overall survival, OS)率、TFS率分别为86%、73%, 但无III级病例。Mathews等^[4]提出III级高危(high risk, HR)的概念: 7岁以上且肝脏体查位于肋下5cm的患者[5年无事件生存(event-free survival, EFS)率为24%]植入失败率(graft failure, GR)、预处理相关毒性(regimen-related toxicity, RRT)、肝静脉闭塞风险均高, 易导致多脏器功能衰竭^[5]。为此, Pesaro小组把Cy剂量下调至160mg/kg, 发现RRT

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[作者简介] 黄楚雯, 女, 硕士, 住院医师。Email: jiang_hua18@sina.com。

降低，但GR却从7%增加至30%^[6]；随后他们加入硫嘌呤及羟基脲，联合氟达拉滨（Flu）及Bu，结果EFS率提高至85%，GR降低至8%^[7]，但至今无其他中心可重复。鉴于Bu增加肝静脉闭塞发生，Gaziev等^[8]提出基于Bu浓度监测进行剂量调整，可降低RRT及GR，但技术开展受限。

苏消安结构与Bu相似，但其水溶性、药物代谢特征均很好，对脏器无剂量限制，为HR患者带来希望^[9]。对比Bu为基础的清髓方案，苏消安/噻替哌（TT）/Flu方案无论在成人TM还是无关供体（unrelated donor, UD）移植中，均有更低的急性移植物抗宿主病（aGVHD）发生率（成人组：31% vs 6.2%；UD：51% vs 23.2%）^[10]。印度有研究发现苏消安/TT/Flu为预处理方案在28例TM患者HSCT中（Ⅲ级患者占75%，HR占39%），OS率为79%，EFS率为72%^[11]。在中国，难以获得苏消安，同时患者不愿接受肝脏活检，无法行Pesaro危险分度。Li等^[12]提出适合中国现状的包

含TT和Bu的NF-08-TM方案和分组标准，OS率达到91.5%，移植相关病死率达8.5%，但仅限于Ⅱ级患者的临床研究。

抗胸腺球蛋白（antithymocyte globulin, ATG）在HSCT中影响外周T细胞池的重建，但可减少GR，同时感染发生率与不含ATG方案相同^[13-14]。而Qin等^[15]却提出含有ATG方案对比不含方案GVHD发生率降低，但感染发生率增高^[15]。Faulkner等^[16]对ATG+Bu+Cy与TT+Bu+Cy预处理方案的对比发现，OS率为94% vs 87%，TFS率为85% vs 80%。巴基斯坦有研究发现Bu+Cy、Bu+Cy+TT、Bu+Cy+ATG方案的OS率分别为76%、81%、86%^[17]。表1总结了预处理方案的演进及评价。

现国际上仍无统一的TM患者HSCT预处理方案。在国内难以获得TT及苏消安的现状下选用何种合适的移植方案，尤其对HR患者，仍需进一步探究。

表1 地中海贫血HSCT预处理方案的演进及评价

文献	预处理方案	患者风险评估	供者类型	OS率	TFS率	评价
Lucarelli 1985 ^[3]	Cy+Bu	n=30, 无Ⅲ级病例	28例为MSD, 2例为全相合父母供体	2年OS率: 86%	2年TFS率: 73%	Cy免疫抑制活性和清髓力均强, 削弱GVHD发生的基础, 促进植入, 但Cy剂量高导致RRT高, 脏器功能不全, 易发生感染, 出血性膀胱炎发生率高
Lucarelli 1996 ^[6]	Cy+Bu	n=115, 均为Ⅲ级病例	均为MFD	5年OS率: 74%	5年TFS率: 49%	Cy剂量减少, RRT降低, GR增高
Sodani 2004 ^[7]	Cy+Bu+Flu+ 羟基脲 + 硫嘌呤	n=33, 均为Ⅲ级病例	均为MFD	6年OS率: 93%	6年TFS率: 85%	增加Flu、硫嘌呤免疫抑制, RRT降低, 羟基脲抑制骨髓增殖, 增加Hb-F表达但无其他中心可重复
Gaziev 2010 ^[8]	Cy+ivBu (基于浓度监测行剂量调整) 联用 / 未用TT 联用 / 未用ATG	n=71, 39例Ⅲ级病例	MSD: 62例, MFD: 9例	3年OS率: 91%	3年TFS率: 87%	能降低RRT及GR, 广泛开展监测Bu浓度在临床上存在困难
Choudhary 2013 ^[11]	TT+ 苏消安 +Flu	n=28, 21例Ⅲ级病例	19例全相合供体, 9例不全相合供体	2年OS率: 78.5%	2年TFS率: 71.4%	苏消安水溶性、药物代谢特征与药物之间反应性均很好, 对肝、肾、心脏等无剂量限制, 但国内难获取
Li 2012 ^[12]	Cy+ivBu+TT+Flu	n=82, 均为NF-08-TM分类Ⅱ级病例	MSD: 30例, UD: 52例	3年OS率: 91.5%	3年TFS率: 87.8%	TT具有免疫抑制、清髓作用, 减少Bu远期毒副作用, 但国内难获取
Faulkner 2017 ^[16]	ATG+Bu+Cy	n=51, 无Ⅲ级病例	MSD: 50例, 全相合母亲供体: 1例	3年OS率: 94%	3年TFS率: 85%	ATG促进植入, 增加感染
Anurathapan 2016 ^[18]	PTIS+ATG+Flu+ivBu+pOS率 t-CY	n=31, 15例Ⅲ级病例	均为Haplo-SCT	2年OS率: 95%	2年TFS率: 94%	供体来源丰富, 促进植入, RRT减少, 但病例数少

注: [OS] 总体生存; [TFS] 无地中海贫血生存; [GVHD] 移植物抗宿主病; [RRT] 预处理相关毒性; [GR] 植入失败率; [Cy] 环磷酰胺; [Bu] 白消安; [Flu] 氟达拉滨; [TT] 噻替哌; [ATG] 抗胸腺球蛋白; [PTIS] 移植前免疫抑制; [pOS-t-CY] 后置环磷酰胺; [MSD] 全相合同胞供体; [MFD] 全相合亲缘供体; [UD] 无关供体; [Haplo-SCT] 单倍体相合供体造血干细胞移植; [Hb-F] 胎儿血红蛋白。

1.2 供体的选择

MSD是HSCT理想供者。Gaziev等^[19]发现MSD移植Ⅲ级患者均成功植入,OS率和TFS率均为92%。但MSD来源受限,MUD、HLA不全相合亲缘供体(mismatched family donor,MMFD)、不全相合无关供体(MMUD)及脐血(umbilical cord blood,UCB)等作为替代供体(alternative donor,AD)应运而生。欧洲协会登记的10年TM患者HSCT中发现MSD、全相合亲缘供体(MFD)、MMFD、UD的2年OS率分别为91%、88%、68%、77%,EFS率分别为83%、78%、68%、77%^[3]。Sun等^[20]以WZ-14-TM方案对48例UD患者(16例为HLA 9/10,4例为8/10,余为全相合)行外周血干细胞移植(peripheral blood hematopoietic stem cell transplantation,PBSCT),OS率及TFS率均为100%,aGVHD和cGVHD发生率均为8.3%^[20]。印度单中心分析全相合UD(MUD)和亲缘供体的PBSCT,发现前者具有更高的GVHD(aGVHD 64% vs 14%; cGVHD 42.9% vs 13.9%)及并发症发生率(感染:71.4% vs 39.5%;非感染并发症:78.5% vs 37.2%),但两者OS率(85.7% vs 87.6%)及TFS率(77.1% vs 84.7%)相仿^[21]。Li等^[22]近期发表的国际多中心研究中发现MFD与MUD移植的5年OS率、EFS率相仿(89% vs 87%; 86% vs 82%),而MMFD与MMUD移植的OS率为73% vs 83%,EFS率为70% vs 78%。我院基于改良NF-08-TM预处理方案比较全相合供体和AD在I、II级患者PBSCT中的预后,两组5年OS率均超过92%,TFS率均超过89%,提示当无全相合供体时,AD也是有效选择(相关数据即将发表)。

Anurathapan等^[18]提出移植前免疫抑制(pre-transplantation immunosuppression,PTIS)1~2个周期后,再行ATG+Bu+Flu为基础的预处理方案,以及后置Cy(+3~+4d),半相合父亲或母亲供体(haploidentical,Hplo)的PBSCT可为没有HLA全相合供体的TM患者,尤其HR患者,提供稳定、持续植入,且严重并发症及GVHD发生率均较低。

综上,首选MSD、MUD均可获得良好预后,被国际指南推荐。有经验单位可尝试开展AD移植。但目前,AD对TM患者HSCT的预后影响,尚需更多随机、前瞻的多中心大样本研究。

1.3 造血干细胞来源的选择

造血干细胞根据来源分为骨髓间充质干细胞(BMSC)、外周血造血干细胞(PBSC)、UCB。PBSCT可缩短植入时间,但比骨髓移植(BMT)具有更高风险的aGVHD和cGVHD^[23]。长期多因素分析提示MSD患者行BMT或PBSCT的15年OS率分别为79.38%、72.97%;TFS率分别为66.85%、69.78%^[24]。脐带血移植(UCBT)具有低GVHD发生率和容易获取的优点,但造血干细胞量少,其有核细胞数目影响粒细胞恢复,CD34⁺细胞数增加可提高成人UCBT的生存率^[25]。一项TM患者HSCT的多中心研究显示PBSCT、UCBT、BMT的OS率分别为83.3%、73.3%、100%,TFS率分别为75.0%、47.1%、100%^[26]。最近我国个别单位开始尝试采用同胞新鲜脐带血联合新生儿一定数量的PBSC或BMSC获得较好的临床效果,但均为会议报告,尚无相关论文发表。

综上,首选BMT,若难以获得情况下予以部分PBSC补充或PBSCT替代亦是安全有效的选择,UCBT尚缺乏经验,TFS率偏低,但新鲜UCBT在能保证供体安全情况下,伦理许可后可实验性开展。

1.4 移植后晚期影响

移植后晚期GR对预后的影响也是不可忽略的问题。Fouzia等^[27]研究中以Bu/Cy为清髓方案的HSCT,1/3患者出现混合嵌合,经治疗仍有1/6混合嵌合患者继续发展成GR,+28d出现混合嵌合的更可能在移植后6个月内出现GR。但在Spitzer等^[28]研究的TM患者HSCT后远期(>15年)的混合嵌合仍有可能形成GR,并再次出现依赖输血状态或转变成骨髓增生异常综合征。

移植后内分泌功能失调、继发肿瘤也给HSCT带来挑战。在法国报道的99例TM患者HSCT中,11%有甲状腺功能障碍,5%患有糖尿病,2%患有心脏衰竭,56%的女性患者及14%的男性患者有性腺功能低下^[29-30]。15例已行HSCT的TM女性患者27次妊娠中,21次自然妊娠顺利;8例移植后男性患者,其生育能力也没有受到影响,提示HSCT后妊娠是安全且可行的^[31]。1例TM女孩,HSCT前取出卵巢组织且被冷冻了14年后,再次移植回自身,通过试管受精,成功生下健康宝宝,提示移植前冻存卵巢组织可保持生育能力^[32]。在中位随访时间为24年的122例HSCT中,8

例出现了继发的实体肿瘤，其5年、10年、15年、30年内发生率分别为1.6%、6.1%、14.9%、13.2%^[33]。

2 基因编辑的自体干细胞移植

基因治疗处于临床实验阶段。通过使用CRISPR/Cas9基因组编辑系统，幼稚的诱导多能干细胞与修饰过的诱导多能干细胞相比，明显提高了基因校正效率^[34]。CRISPR/Cas9基因编辑系统将Cas9核蛋白和腺病毒载体结合在一起，实现在造血干细胞中血红蛋白 β 基因的同源重组^[35-36]。用修饰过的 β -珠蛋白基因转导干细胞后的自体移植在少数患者中已获得成功，但需要大量临床试验予以证明^[37-38]。整合的HAd5/35++腺病毒载体表达抗CRISPR肽可以减少CRISPR/Cas9毒性，为血红蛋白疾病的造血干细胞基因治疗提供一个新的平台^[39]。子宫内基因治疗可纠正杂合地中海贫血小鼠模型，未来或许可为怀孕妈妈带来福音^[40]。减少清髓毒性及降低费用仍是基因编辑的自体干细胞移植面临的挑战^[41]。

3 结论与展望

HSCT仍是TM唯一的治愈手段，但最佳的预处理方案尚无结论，尤其针对Ⅲ级HR患者；有MSD需尽早移植以获得最佳的预后，AD在一定程度上扩大了患者的供体选择，在Ⅰ、Ⅱ级患者的应用中也可与MSD移植的预后相媲美；干细胞来源可选择BMSC或PBSC，但无关UCB并非推荐的选择；移植后仍需监测内分泌的远期影响；基因治疗给患者带来曙光，但远期的影响尚需探讨。

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