·综 述·

造血干细胞移植植入失败的研究进展

尹光丽,李建勇,缪扣荣*

南京医科大学第一附属医院血液科,江苏 南京 210029

[摘 要] 造血干细胞移植是治疗造血系统恶性肿瘤及某些遗传性疾病的重要手段,其中造血及免疫功能重建是移植取得成功的基础。植入失败是造血干细胞移植取得成功的一个主要障碍,并且严重危及患者的短期生存。随着人类白细胞抗原不相合或半相合移植及减低剂量预处理技术越来越广泛的应用,植入失败的发生率也随之增加。对植入失败发病机制的深入研究和更大数据的临床分析,发现并鉴定植入失败的重要预测指标,可帮助我们早期预防这一重要并发症的发生。文章拟对造血干细胞移植植入失败的概念、发病机制、相关影响因素及治疗手段等方面的最新进展作一综述。

[关键词] 造血干细胞;植入失败;免疫介导;供者淋巴输注

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Progress on graft failure of allogeneic hematopoietic stem cell transplantation

YIN Guangli, LI Jianyong, MIAO Kourong*

Department of Hematology, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China

[**Abstract**] Hematopoietic stem cell transplantation (HSCT) is an important method to treat hematopoietic malignancies and some inherited diseases. Hematopoietic and immunological reconstitutions are the basis of successful transplantation. One significant obstacle to the success of HSCT is represented by graft failure, which severely endangers patients' short-term survival. As human leukocyte antigen mismatched or haploidentical transplantation, and reduced intensity conditioning technology are more and more widely carried out, the incidence of implant failure increasing. With the study of the mechanism of implant failure and the clinical analysis of larger data, identifying important predictors of implant failure can help us to prevent this important complication of hematopoietic stem cell transplantation early. Here, we provide an overview on the recent advances in the concept, pathogenesis, related factors and treatment methods of hematopoietic stem cell engraftment failure.

[**Key words**] hematopoietic stem cell; graft failure; immune mediated; donor lymphocyte infusion

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造血干细胞移植(hematopoietic stem cell transplantation,HSCT)是治疗造血系统恶性肿瘤、自身免疫性疾病、淀粉样变性及某些遗传性疾病的重要手段,其中造血及免疫功能重建是移植取得成功的基础。移植物抗宿主病(graft versus host disease,GVHD)、疾病复发、移植物植入失败等并发症成为移植失败的主要原因,移植物植入失败严重危及患者的短期生存[1]。随着人类白细胞抗原(human leukocyte antigen,HLA)不相合或半相合移植及减低剂量预处理(reduced intensity conditioning,RIC)技术越来越广泛的应用,植入失败的发生率也随之增加[2-3]。在减低剂量预处理条件下,植入失败的发生率为5%~30%;清髓性预处理(myeloablative conditioning,MAC)植入失败的发生率相对较低,为1%~5%。脐血移植植入失败的发生率最高达10%~30%,HLA全相合无关供者外周血干细胞移植植入失败的发生率为4%[4]。该并发症发生率虽然相对较低,但一旦发生处理非常棘手且预后极差。本文拟对造血干细胞植入失败的概念、发病机制、相关

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*通信作者(Corresponding author),E-mail:kourongmiao@163.com

影响因素及治疗手段等方面的最新进展作一综述。

1 植入失败的概念

造血干细胞移植后造血重建标准：连续3 d外周血中性粒细胞绝对计数≥0.5×10^{9}个/L为粒系造血重建；血小板计数＞20×10^{9}个/L，且连续7 d不依赖血小板输注为巨核系造血重建[5]。性染色体转变、血型转变、短片段串联重复（short tandem repeat，STR）转为供者型亦为植入成功标志[6]。动态监测受者嵌合状态亦可初步判断植入情况。嵌合状态是指供受者双方造血细胞达到共存的现象，完全嵌合或混合嵌合分别指供者细胞占受者骨髓或外周血比例＞95%或5%~95%[7-8]。移植植入失败可分为原发性植入失败和继发性植入失败。原发性植入失败指以外周血干细胞或骨髓干细胞作为移植物来源移植后28 d未达植入状态，或以脐带血干细胞来源移植后42 d未达者；而继发性植入失败指达到成功植入标准后再次出现三系中至少两系的血细胞下降或丢失供受者嵌合状态[3,9]。有研究报道较继发性植入失败，原发性植入失败有相对更高的死亡率[10]。

2 植入失败的发病机制

植入失败的主要原因为受者针对供者细胞发生免疫反应，即移植物被排斥，与受者体内残存的免疫细胞及特异性抗体对供者移植物的免疫排斥反应密切相关。此外，一些非免疫性因素也参与了移植物被排斥的过程。

2.1 免疫介导因素

参与其中的细胞免疫排斥因素主要包括受者T细胞、自然杀伤（nature killer，NK）细胞及体液免疫介导的抗供者特异性HLA抗体[4]，也有一些研究报道抗供者CD34/VEGFR-2抗体也是导致植入失败的关键因素[11-12]，尤其在HLA不相合移植物去T细胞（T-cell-depleted，TCD）及减低剂量预处理移植过程中[13]。

2.1.1 T细胞介导

在供受者HLA不相合条件下，多数研究认为受者残存的T细胞介导的细胞毒性反应是移植物排斥的始动因素[3]。移植前患者多次输注血液制品，受者体内被同种异体抗原所致敏，产生抗供者细胞毒性T细胞。当输注造血干细胞时，CD8$^+$ T细胞作用于供者主要或次要组织相容性抗原进而杀灭移植物中造血干细胞[14]。特别是在HLA半相合去T细胞移植中，移植物去T细胞后无法清除受者体内残存的CD8$^+$T细胞。受者体内CD8$^+$T细胞通过穿孔素、颗粒酶B及FasL介导的细胞毒性引起移植物植入失败的风险大大增加[15]。

2.1.2 NK细胞介导

NK细胞表面的杀伤细胞免疫球蛋白样受体（killer cell immunologlobulinlike receptor，KIR）属于免疫球蛋白超家族[16]，分为抑制性受体（inhibitory KIR，iKIR）及活化性受体（activating KIR，aKIR）。KIR与靶细胞上主要组织相容性复合物（major histocompatibility complex，MHC）分子相互作用调节NK细胞功能。基于“自我丢失”的识别作用及“配体-受体”结合模式，当预处理后残留的受者KIR所识别供者HLA配体缺失时，向NK细胞传递活化信号，激活NK细胞攻击溶解靶细胞[17]。在异基因造血干细胞移植（allogeneic hematopoietic stem cell transplantation，allo-HSCT）之前，接受一定剂量的放疗消耗受者NK细胞，有助于移植物植入[18]。相反，供者KIR受体与受者HLA配体不相合时，供者aKIR传递的激活信号无法被iKIR抑制，引起NK细胞同种异源反应活性清除肿瘤细胞，有利于移植物植入，同时预防GVHD[19]。KIR受体-HLA配体在HSCT植入失败及GVHD间尚有很多不解之处，影响临床转归。

2.1.3 特异性抗体介导

移植前接受多次输血的患者接受移植后发生移植物排斥风险较大，受者体内产生高水平的反应性抗体介导的体液免疫是移植物排斥的主要原因，且这种抗体无法被移植前预处理消除掉。输血致敏后受者体内产生特异性反应性抗体，与造血干细胞表面HLA抗原结合，通过补体依赖的细胞毒性（complement dependent cytotoxicity，CDCC）及抗体依赖的细胞介导的细胞毒性（antibody-dependent cell-mediated cytotoxicity，ADCC）免疫损伤途径杀伤造血干细胞，发生移植物排斥的风险与靶抗原密度及抗体FC段结合能力有关[20-23]。

2.2 非免疫介导因素

血液肿瘤患者在进行HSCT前往往接受过长期大剂量的放、化疗，其和造血衰竭性疾病都可损伤骨髓基质细胞，严重影响移植物的归巢、定植和增殖。基质细胞的损伤造成许多生长因子及细胞因子的缺乏，例如转化生长因子β（TGF-β）、白细胞介素6（IL-6）、前列腺素E2（PGE2）、肝细胞生长因子（HGF）及吲哚胺2，3-二氧化酶（IDO）等，共同介导

移植物植入失败[24-25]。目前非免疫介导因素在植入失败中的病理生理机制尚未被完全阐明，有待进一步研究。

3 植入失败的影响因素

HLA不相合或半相合及非清髓性预处理(non-myeloablative，NMA)技术的广泛开展，移植并发严重感染特别是病毒(巨细胞病毒、人类疱疹病毒-6、细小病毒等)感染的发生，移植物排斥或植入失败的发生率明显升高[10]。影响因素主要包括供受者HLA及ABO血型相合度、预处理方式、移植物来源及植入细胞数量等方面。

3.1 供受者HLA及ABO血型相合度

选择无关供者作为HSCT供者来源时，供受者HLA的相合度是影响移植物成功植入的最重要因素。供受者HLA-Ⅰ类抗原不合其移植物排斥发生率较高，而DQ和DP位点不合对移植物植入有无影响观点尚不统一[26-27]。国内有学者[23]分析大量数据建议，接受HLA半相合或不相合HSCT前，筛查受者体内HLA抗体，尤其抗供者HLA特异性抗体，对预测移植物是否成功植入至关重要。另大量研究数据已经证实ABO血型不合并不引起植入失败的发生，对受者的最大影响是造成红系植入缓慢，甚至发生纯红细胞再生障碍性贫血[28]。但在非亲缘脐血移植中的移植结果尚存在不同意见[29-30]。Remberger等[31]对既往就诊于卡罗琳斯卡大学医院的224例ABO血型不合患者进行调查，结果示ABO血型相合及不合发生植入失败率分别为7.5% *vs*. 0.6%(P=0.02)，多因素分析显示，移植物植入失败与ABO血型不合(P=0.008)及HLA不相合(P=0.03)有关。

3.2 预处理方式选择

考虑到MAC预处理带来较高的移植相关死亡率(transplant related mortality，TRM)，尤其对于老年及年轻合并器官功能衰竭患者，RIC在HSCT中得到广泛应用。因受者体内残存免疫细胞，随之而来并发植入失败发生率明显升高[32]。Olsson等[10]研究显示接受MAC、RIC及NMA的HSCT发生植入失败率分别为3%、8%和19%，多因素分析示选择NMA作为预处理方式植入失败发生率显著高于RIC(P<0.01)及MAC(P<0.01)。Slot等[32]对53例骨髓纤维化患者接受不同预处理方式的植入失败发生率进行研究，接受NMA预处理后HSCT第60天中性粒细胞植入率为56%，较RIC(84%)显著降低(P=0.03)，再次验证了NMA导致植入失败的发生率增加。

3.3 移植物来源

脐血移植较骨髓及外周血造血干细胞移植具有免疫原性弱，HLA相合度要求相对较低，T细胞相对不成熟，GVHD发生率低[33]等优点。但由于造血干细胞数量较少，造血重建及免疫重建明显延缓，植入失败发生率较高[34]。相关文献报道脐血移植引起的植入失败率高达20%以上，而骨髓及外周血干细胞移植的植入失败发生率相对较低，经粒细胞集落刺激因子(G-CSF)动员的外周干细胞作为移植物来源，$CD34^+$细胞数量较高，T细胞、B细胞、NK细胞和单核细胞的数量增加至少10倍，造血及免疫重建更快，但急性或慢性GVHD发生率较高。Zhang等[35]进行Meta分析表明脐血移植的植入失败发生率显著高于骨髓及外周血造血干细胞移植(P<0.001)。

3.4 移植物干细胞数量

移植物中有核细胞及$CD34^+$细胞含量的多少直接影响移植物是否能成功植入，尤其在脐血移植中更为突出。Olsson等[10]研究示接受有核细胞低于2.5×10^8个/kg及$CD34^+$细胞低于3×10^6个/kg的移植，其植入失败的发生率显著升高，分别为10%(P<0.01)和12%(P<0.001)，多因素分析结果显示移植物中有核细胞≥2.5×10^8个/kg可明显减少植入失败的发生。

4 植入失败的防治策略

4.1 二次移植

植入失败，不管是原发性或继发性，最有效的治疗措施是接受挽救性的二次移植。但选择二次移植延长总生存面临着诸多挑战：选择相同供者或其他供者、预处理方式、干细胞来源及二次移植前合并活动性感染或Karnofsky/Lansky评分较低等。优化二次移植方案对提高植入失败患者再次移植后总体生存率十分必要。目前尚无明确数据证实相同供者或者新供者有助于二次移植的成功或者提高生存率。鉴于首次移植受者免疫介导的移植物排斥，学者们常推荐优先选择相对合适的另一供者作为移植供者[3]。学者们分析影响植入失败因素并寻找合适的预处理方案提高移植物植入率，接受二次移植的患者在经历首次移植物排斥后应该接受降低剂量高度免疫抑制预处理方案清除宿主淋巴细胞，例如氟达拉滨(Flu)、环磷酰胺(CTX)、抗人胸腺细胞球蛋白(ATG)以及必要的全身照射(total body irradiation，TBI)[3,36-38]。

二次移植移植物来源与能否成功植入及预后

密切相关。日本学者为比较接受挽救性二次移植时不同干细胞来源对再次植入及预后的影响，回顾性分析了220例既往接受脐血移植植入失败的患者[39]。选择再次脐血移植患者30 d中性粒细胞植入率为39%，外周血干细胞及骨髓干细胞植入率分别为71%（$P<0.001$）和75%（$P=0.016$），选择外周血干细胞作为二次移植物来源较脐血干细胞，1年非复发死亡率明显降低（$P=0.019$），并具有较高的总体生存率（$P=0.036$）。而面临缺少HLA相合同胞供者及无关供者，学者也进行了脐血移植挽救植入失败患者，且初见成效。二次移植移植物的选择，需根据有无合适供者、供者所提供干细胞数量等具体实际情况作出选择，且相关临床研究尚未得出结论性结果，需进一步探究。选择二次移植挽救治疗植入失败患者面临的问题较多，需要临床医师结合受者与供者情况制定最佳方案。

4.2 间充质干细胞输注

间充质干细胞（mesenchymal stromal cell，MSC）可以从人体多种组织中分离出来，例如骨髓、血液、脐带血、胚胎组织等。MSC被认为是骨髓基质细胞的前体细胞，为造血提供支架，促进造血植入，在调控造血与免疫功能方面担任重要的角色。接受HSCT的患者输注MSC不仅有助于造血干细胞的植入，预防移植物排斥，而且减轻GVHD的发生[40]。Kuzmina等[25]对接受allo-HSCT持续移植物植入失败的患者单纯输注供者骨髓MSC，2周后所有患者造血功能恢复，受者骨髓中监测到供者MSC。多个研究报道输注MSC是安全的，均无不良事件发生。国内韩忠朝教授多次研究HLA半相合移植（haplo-HSCT）联合第三方脐血间充质干细胞（UC-MSC）输注治疗血液系统疾病疗效。一项对50例复发难治的恶性血液肿瘤进行Haplo-HLA联合UC-MSC共移植研究，所有患者移植物均成功植入；其中粒细胞及血小板重建的中位时间分别为12 d和15 d[41]。MSC促进造血细胞植入，可能与MSC分泌多种细胞因子及通过多条信号通路相互作用促进造血干细胞归巢及增殖有关[42]。动物体内实验研究证实MSC联合细胞因子可成功培养并扩增造血祖细胞[43]。

4.3 药物预防及细胞治疗

采取针对性措施预防植入失败比治疗更具临床价值，例如环孢素、CTX、ATG、抗CD52单抗等有效进行受者免疫抑制并预防植入失败[44-46]。对于因移植前多次输注红细胞植入失败风险高的患者需增加预处理强度，如增加Flu及TBI处理。选择使用G-CSF动员外周血干细胞作为移植物来源、再生障碍性贫血患者移植前预处理联合使用ATG及CTX增强免疫抑制，均可增加移植植入率。

细胞治疗主要涉及到的是供者淋巴细胞输注（donor lymphocyte infusion，DLI）。DLI常用于治疗allo-HSCT后疾病的复发，尤其是分子复发。研究者们发现DLI能提高宿主的嵌合率并且减少移植物植入失败[3]。Mohamedbhai等[44]回顾性分析了以阿伦单抗预处理的allo-HSCT，27例可评估病例中，3例无嵌合状态，其余为混合嵌合体，接受DLI后均转变为完全嵌合，这表明DLI治疗移植物排斥临床有效，但也易引起致命的GVHD[47]。二者之间的抉择需经验丰富的临床医师作出判断。输注淋巴细胞的时机尚无明确定论，专家们推荐受者来源的造血细胞快速增长或怀疑移植物排斥且无GVHD时予以及时输注[3]。

4.4 增加移植物干细胞

脐血移植与骨髓或外周血造血干细胞相比，因其独特的低GVHD、较强的增殖优势及低HLA相合度要求，在儿童恶性血液病中应用较为广泛。但由于单份脐带血中有核细胞及造血祖细胞含量较低，成人移植中常常导致植入延迟，甚至植入失败[48]。寻找新的方法增加干细胞的数量十分必要，包括使用双份脐带血、脐带血联合去T细胞的单倍型供体干细胞移植及体外扩增脐血干细胞[49-50]。近期通过体外扩增脐血细胞试图提高造血祖细胞或$CD34^+$细胞量的研究较为火热，其中体内外试验验证的Notch配体hDlR蛋白促进$CD34^+$细胞有效增殖并且成功植入[51]。此外，SR-1（stem regenin 1）作为芳烃受体（aryl hydrocarbon receptor，AhR）抑制剂，相关的体外研究显示可使有核细胞增加11倍，$CD34^+$细胞增加73倍，其作为一种新的扩增脐血干细胞单独移植Ⅱ期临床试验已经完成。国外相关研究对17例接受脐血移植患者的供者干细胞进行SR-1培养处理，其中$CD34^+$较扩增前增加330倍，有核细胞增加854倍，17例患者均成功植入且植入时间较未处理过的脐血干细胞明显缩短，证实了通过SR-1扩增脐血造血干细胞安全有效[52]。

5 小结与展望

移植物植入失败的发生主要与免疫因素相关，其发生率虽相对较低，但严重影响了移植患者的长期生存。评估移植患者状态并发现可能出现植入失败的相关因素，继而选择最佳的方法预防并治

疗,可减少此类并发症的发生。一旦发生植入失败,尽快完成二次移植是目前公认的主要解决方案。MSC可促进造血细胞植入,DLI可增强供者来源细胞的免疫能力,抑制受者来源细胞的增长,从而减少植入失败的发生。随着植入失败发病机制的深入研究和更大数据的临床分析,发现并鉴定植入失败的重要预测指标,可帮助我们早期预防这一重要并发症的发生。

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