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骨髓增生异常综合征异基因造血干细胞移植的预处理方案的现状

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摘　要

骨髓增生异常综合征是一种起源于干细胞的异质性骨髓疾病，其临床表现和预后各异。随着基因组学和高通量测序技术的飞速发展，对MDS的预后做出了新的分层分期，对于高风险的MDS患者，治愈这种疾病的唯一方法为异基因造血干细胞移植，但确定最佳的移植前预处理方案仍是一个未得到有效解决的问题。本文综述了现有的预处理方案，并讨论了针对预处理方案的前沿探索。未来，通过药物发展和个体化治疗策略的不断完善，有望提出更加平衡低毒性和有效抗肿瘤作用的预处理方法。

关键词

骨髓增生异常综合征，异基因造血干细胞移植，预处理方案

Current Status of Preconditioning Regimens for Allogeneic Hematopoietic Stem Cell Transplantation in Myelodysplastic Syndromes

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Abstract

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell

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disorders characterized by diverse clinical manifestations and variable prognoses. With rapid advancements in genomics and high-throughput sequencing technologies, novel prognostic stratification systems have emerged for MDS. For high-risk MDS patients, allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative treatment, yet determining the optimal pre-transplant conditioning regimen continues to pose significant clinical challenges. This review summarizes existing conditioning approaches and explores cutting-edge research in regimen development. Looking ahead, continued progress in pharmaceutical innovation and refinement of personalized treatment strategies may enable the design of conditioning protocols that better balance reduced toxicity with maintained anti-leukemic efficacy.

Keywords

Myelodysplastic Syndromes, Allogeneic Hematopoietic Stem Cell Transplantation, Preconditioning Regimens

1. 概述

骨髓增生异常综合征(Myelodysplastic Syndromes, MDS)是一组起源于能够进行髓系和淋巴分化的多能干细胞的异质性克隆性疾病，其特征是骨髓造血缺陷和髓内细胞凋亡的发生[1] [2]。但 MDS 的明确发病机制仍未完全了解，越来越多的证据表明，内在机制可能涉及炎症和先天免疫失调[3]、细胞凋亡失调[4]。MDS 最终结局为感染、出血、转化为 AML 或疾病进展[5]。根据美国北美癌症登记协会(SEER)数据，MDS 的年龄调整发病率为每年每 10 万人 4.8 例[6]。MDS 在老年人群中发病率更高，中位发病年龄为 72 岁，80 岁以上患者的年发病率高达 55.5/10 万[7]。在 40 岁以下的人群中，发病率比较低，小于 14 岁的儿童和青少年 MDS 占血液系统疾病不到 5% [8]-[12]。

2012 年 MDS 预后国际工作组(IWG-PM)基于细胞遗传学分组，提出 IPSS-R 积分系统，它使用细胞遗传学和血液学参数，包括染色体核型、骨髓原始细胞计数、血红蛋白水平、血小板计数和中性粒细胞绝对计数，将 MDS 区分为极低危至极高危的 5 个危险度分层[13]。

根据 IPSS-R 积分系统，低风险 MDS 患者包括分类为极低风险、低风险和中等风险(评分 ≤3.5 分)的患者[14]。此类患者的治疗目标通常为减轻症状、改善患者的生活质量、减少输血负担和预防其他并发症，例如铁超负荷、感染或出血。观察被普遍认为是无症状低危患者的首选治疗方式。高风险 MDS 患者包括分类为中危(评分大于 3.5)、高危或极高危[15]。与低风险 MDS 相比，高风险 MDS 的预后较差，白血病转化时间更短，总生存期更短，且治疗通常在诊断为高风险 MDS 时进行[16]。

高风险 MDS 治疗中，去甲基化药物(Hypomethylating Agents, HMA)虽然是不宜行造血干细胞移植的高风险 MDS 患者的一线药物，但只有约 50%的患者对这些药物有反应。此外，无反应的患者可产生耐药性，导致预后更差[17]。化疗可能是高风险 MDS 患者的另一种治疗选择，然而，已经证明化疗对高危核型患者没有益处[18]。对于高风险且符合造血干细胞移植条件的 MDS 患者，异基因造血干细胞移植(Allogeneic hematopoietic stem cell transplantation, Allo-HSCT)是 MDS 唯一可能治愈的治疗选择。Allo-HSCT 可以使患者从高剂量化疗和移植物抗白血病(Graft versus Leukemia, GVL)效应中受益，这可能有助于根除 MDS 克隆。Allo-HSCT 的生存获益不仅适用于体能状态良好的年轻患者，也适用于老年患者[19]。

然而 Allo-HSCT 中，确定最佳的移植前预处理方案仍是一个未得到有效解决的问题。

2. 不同预处理方案在骨髓增强异常综合征中的应用

2.1. 异基因造血干细胞预处理的意义

1) 清除肿瘤细胞：预处理通过大剂量的化疗和(或)放疗，最大限度地清除患者体内的肿瘤细胞，减少肿瘤负荷，为造血干细胞的移植创造条件[20] [21]。

2) 抑制免疫系统：预处理方案中的化疗和放疗会破坏患者的免疫细胞，特别是 T 淋巴细胞，从而降低免疫系统的活性，减少其对移植的造血干细胞的排斥反应[22]。

3) 创造适宜的造血微环境：预处理会破坏患者原有的造血微环境，去除竞争性的宿主造血干细胞，为移植的造血干细胞提供一个适宜的生存和增殖环境[23]。

4) 降低移并发症：通过合理的预处理方案设计，调节患者的免疫状态，减少过度炎症反应，降低 GVHD 的发生概率[24]。

2.2. MAC 方案在 MDS 中的应用

MDS 的异基因移植清髓性预处理(myeloablative conditioning, MAC)旨在通过强烈的化学治疗或放射治疗彻底摧毁受者的骨髓，以最大程度地减少疾病的复发，并为新的造血干细胞提供生长空间[25]。具体使用方案包括：

1) 白消安联合环磷酰胺(BU/CY 方案)：白消安予以 0.8 mg/kg 的剂量，每日四次，共静脉滴注 2 至 3 天，总剂量为 9.6 至 12.8 mg/kg；环磷酰胺予以 1.5 g/m^2，每日一次，共静脉滴注 2 天，总剂量为 3 g/m^2 [25]。

2) 全身照射联合环磷酰胺(TBI/CY 方案)：全身照射总剂量一般在 7.7 至 16 Gy，分 1 至 12 次进行；环磷酰胺予以 60 mg/kg，每日一次，共静脉滴注 2 天，总剂量为 120 mg/kg [25]。

这种类型的预处理方案在 MDS 患者中表现出显著的降低复发率和提高生存率[26]的优点，同时也存在较高移植相关死亡率(Transplant-related mortality, TRM)和长期免疫抑制的不良预后结果[25]。因为其毒性和潜在的严重副作用较大，故适用于年龄较轻、身体状况较好、疾病进展较快的患者，以最大限度地清除肿瘤细胞，提高移植成功率。

2.3. RIC 方案在 MDS 中的应用

MDS 的异基因移植减低强度预处理方案(Reduced-Intensity Conditioning, RIC)旨在降低传统清髓性预处理的毒副作用，同时保持对疾病的控制能力。具体使用方案包括：

1) 以氟达拉滨为基础联合白消安、环磷酰胺等药物：氟达拉滨予以 30 mg/m^2 的剂量，静脉滴注连续 5 天，总剂量为 150 mg/m^2；白消安(Bu)：白消安予以 0.8 mg/kg 的剂量，每日四次，共静脉滴注 3 天，总剂量为 12.8 mg/kg。

2) 低剂量全身照射联合环磷酰胺、氟达拉滨等药物：全身照射总剂量 2 Gy，单次或分次进行；环磷酰胺予以 60 mg/kg，每日一次，共静脉滴注 2 天，总剂量为 120 mg/kg，或氟达拉滨予以 30 mg/m^2 的剂量，静脉滴注连续 5 天，总剂量为 150 mg/m^2 [26]。

这种类型的预处理方案通过降低化疗和放疗的剂量，显著减轻了对重要器官的功能损害，由于毒性降低，移植后的造血恢复较快，故患者可尽快脱离骨髓移植后的脆弱期，移植相关死亡率也相应下降。并且低剂量全身照射(TBI)在 RIC 方案中发挥了重要的免疫调节作用，有助于控制移植物抗宿主病(graft versus host disease, GVHD)的发生[27]。但 RIC 方案的化疗和放疗剂量降低，对肿瘤细胞的杀伤力减弱，可能导致更多的肿瘤细胞残留在体内，这增加了疾病复发的风险，尤其是在高危 MDS 患者中更为明显。

如果患者疾病复发，后续的治疗选择会更加有限，治疗难度更大，效果更差。由于 MDS 通常在中老年患者中被诊断出来，因此在某些情况下已被 RIC 取代 MAC。

2.4. 药物免疫学机制对比分析

在 MDS 造血干细胞移植预处理中，白消安、氟达拉滨、TBI 及环磷酰胺通过免疫抑制与肿瘤清除的双重机制发挥作用：白消安和环磷酰胺作为烷化剂，通过破坏 DNA 合成抑制免疫细胞增殖，前者对髓系肿瘤具有特异性，后者兼具广谱抗肿瘤作用且成本低廉；氟达拉滨作为嘌呤类似物，不仅阻断淋巴细胞 DNA 复制以降低 GVHD，还可通过改善调节性 T 细胞比例维持免疫稳态；TBI 则通过电离辐射直接诱导淋巴细胞凋亡，实现高效肿瘤清除，但对非造血器官(如肺、肝)存在非靶向毒性。尽管上述药物均能有效降低 GVHD 发生率和肿瘤复发风险，但其临床应用受限于显著毒性：白消安可能诱发第二肿瘤且单药强度不足，氟达拉滨易导致重度骨髓抑制和感染风险，TBI 增加慢性 GVHD 风险，环磷酰胺则因肠道毒性和剂量依赖性肾损伤受限。研究表明，TBI 适用于高危 MDS 患者，氟达拉滨在免疫调控中更具优势，而白消安与环磷酰胺常作为联合方案的基础药物。最终用药策略需结合患者疾病分层(如 IPSS-R)、基因突变(如 TP53)及器官功能状态进行个体化优化，以平衡疗效与安全性[25]-[28]。

3. 新型预处理方案的探索与研究

3.1. 曲奥舒凡与白消安

曲奥舒凡(Treosulfan)是一种烷化剂，在欧洲国家首次被批准用于治疗卵巢癌[29]，现已被评估纳入各种血液系统恶性肿瘤中 Allo-HSCT 的预处理方案用药[30]。针对 MDS 和继发性髓系白血病(Acute Myeloid Leukemia, AML)，有予以曲奥舒凡作为预处理药物使用的临床实验，所有患者均成功移植，并观察到非常低的急性移植物抗宿主病(Acute Graft-versus-Host Disease, aGVHD)的发生率，II 级以上的 aGVHD 的发生率约为 23% [31]。一项回顾性真实世界多中心研究中提出：对于患有 MDS 的成年人，如初次耐药或继发急性髓系白血病，采用曲奥舒凡联合氟达拉滨的预处理方案，可获得较好的移植成功率和较低的不良反应率[32]。并且有研究指出曲奥舒凡联合氟达拉滨预处理方案既保留了清髓作用，也降低了骨髓毒性[33]。其临床应用需实施个体化给药方案，剂量调整应基于以下多维度评估指标：患者年龄、体重指数、肾功能状态及肝功能分级。一项回顾性研究表明：奥舒凡联合氟达拉滨预处理方案拥有类似于 MAC 的低复发率和类似于 RIC 的低 TRM，这表明使用奥舒凡联合氟达拉滨预处理方案进行 Allo-HSCT 的 MDS 患者改善了总生存期[34]。

3.2. 添加噻替哌

噻替哌是另一种烷化剂，历史上一直用于脐带血移植[35]，以改善造血干细胞移植效果，同时减少化疗相关的毒性。一种由噻替哌－白消安－氟达拉滨(TBF)组成的 MAC 预处理方案与进行 Allo-HSCT 的 AML 患者的复发率降低有关[36] [37]，但没有针对 MDS 患者的证据。虽然，在接受同种异体造血干细胞移植的 AML [38]和 MDS [39]患者中评估了基于噻替哌－曲硫安－氟达拉滨(TTF)的预处理方案，提示患者的 RFS、OS 均延长，但无法根据这些研究提出强有力的推荐。

3.3. 调节免疫重建

除了因 MDS 患者年龄、合并疾病较多所致选用 RIC 预处理方案外，3 个月时完全供体 T 细胞嵌合体已被报告为移植物对抗骨髓发育不良、白血病效应的潜在生物标志物[40]。目前，非亲缘供者外周血干细胞移植的 GVHD 预防多选用抗胸腺细胞球蛋白(anti-thymocyte globulin, ATG)或环磷酰胺[41]，有报道表示：ATG 与移植物抗宿主病和无复发生存期(GRFS)改善相关[42]。

3.4. 添加去甲基化药物

去甲基化药物(Hypomethylating Agents, HMA)可以增加白血病细胞膜上的 HLA、次要组织相容性抗原和 KIR 配体，分别可以增强 CD8 + T 细胞和 NK 细胞毒性。一项回顾性研究中，使用地西他滨治疗的患者并未有明显改善的 RFS、OS。只有一项亚组分析表明，IPSS-R 较高的患者有降低复发率的趋势(P = 0.085) [43]。在 MAC 预处理方案中加入维奈托克和地西他滨的研究已进行短期随访。然而，100 天内的发生率非常高，III 级以上的 aGVHD 的发生率为 26% [44]。

3.5. 个体化预处理方案调整

在 MDS 造血干细胞移植中，个体化预处理方案的探索聚焦于优化免疫抑制与肿瘤清除的平衡，主要包括以下策略：含地西他滨的方案通过 DNA 甲基化抑制剂作用促进肿瘤细胞分化，上调肿瘤相关抗原表达以增强 T 细胞介导的抗肿瘤免疫，并通过调节调节性 T 细胞数量减轻 GVHD，同时联合传统清髓方案可增强 GVL 效应，降低复发率；白消安联合氟达拉滨通过烷化剂与嘌呤类似物的协同作用实现双重免疫抑制及肿瘤清除，显著降低 GVHD 风险并提高移植成功率；ATG 通过抑制 T 细胞活性及诱导免疫耐受双重机制减少 GVHD 和排斥反应；其他方案如环磷酰胺联合阿糖胞苷通过抑制 DNA 合成发挥抗肿瘤及免疫调节作用，G-CSF 则通过刺激造血干细胞增殖和免疫功能调节提高采集效率。研究表明，个体化预处理需综合评估患者年龄、疾病亚型、基因突变及器官功能状态，针对性选择方案以平衡疗效与毒性[45]。

4. 总结

尽管 MDS 已经根据遗传生理病理学的不同分子组进行了更好的分类和理解，但 Allo-HSCT 仍然是持久疾病控制的最佳治疗选择[46]。首先，现有的预处理方案，均不能在延长患者无进展生存期(PFS)、总生存期(OS)基础上有效降低患者 TMR 之间取得突破。其次，烷化剂仍然是 MDS 预处理方案的主要方案，没有前瞻性稳健的试验表明噻替哌或美法仑可以改善患者的预后。曲奥舒凡作为白消安的理想替代品，其最佳剂量和最佳联合策略需要进一步研究，特别是关于原发性移植失败的潜在风险。第三，MDS 移植后复发率高可能归因于 MDS 克隆和肿瘤微环境的化学敏感性较低。虽然 HMA 可能通过同时诱导调节性 T 细胞来调节 GVHD [47] [48]，但在 RIC 方案中，只有少数研究将 HMA 纳入预处理方案，随机研究中尚未证明 HMA 具有很强的益处[49]。Allo-HSCT 的有效性仍然取决于一种平衡低毒性和有效抗肿瘤作用的预处理方法。

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