·综　述·

淋巴瘤自体造血干细胞移植的临床实践优化探索与未来展望

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［摘要］自体造血干细胞移植（autologous hematopoietic stem cell transplantation，AHSCT）是高度侵袭性和复发/难治性淋巴瘤的有效治疗手段之一，可为患者带来生存获益。近年来，小分子靶向药物、单克隆抗体、细胞治疗和免疫治疗等新药给淋巴瘤患者提供了更多的选择，但AHSCT在淋巴瘤治疗中仍占据重要地位。对AHSCT适应证和治疗时机进行概述，进而详细介绍AHSCT治疗流程、移植后管理及注意事项。AHSCT的适应证和治疗时机与疾病亚型、危险分层及移植前疾病状态紧密相关。行AHSCT前，需对患者进行移植前诱导及疗效评估，诱导方案根据淋巴瘤亚型不同而有所差异，可参考相应指南推荐进行选择；目前临床中广泛使用的疗效评价标准为影像学缓解（CT/MRI评价）和代谢缓解（PET/CT评价）。AHSCT流程的每一个环节都与预后密切相关，整体流程包括干细胞动员及采集、移植前预处理、干细胞回输、合并症管理、植入情况评估。制定良好的动员策略以保证动员效果是最关键的一步，对于淋巴瘤患者，应根据诱导治疗后患者的疾病缓解状态来选择最佳的动员方案，以提高干细胞动员成功率。参考国外造血干细胞动员经验，在疾病稳定状态下，如达到CR1/CR2的患者，可优选稳态动员；针对活动复发的患者，建议优选疾病特异性的非稳态动员。针对干细胞采集目标，过往国内外临床经验多推荐外周血干细胞（peripheral blood stem cells，PBSC）的最佳目标采集量为5×10^6个$CD34^+$细胞/kg，近期新发表的研究结果提示，骨髓瘤患者PBSC为4.5×10^6~8×10^6 个$CD34^+$细胞/kg具有更好的生存获益，淋巴瘤患者PBSC最佳阈值还有待进一步研究。自体移植物质量评价也打破了传统仅评估$CD34^+$细胞数量的模式，已有研究显示，可将自体移植绝对淋巴细胞计数（autograft absolute lymphocyte count，A-ALC）纳入到自体移植物评估中。AHSCT预处理应采用清髓性预处理方案，BEAM（卡莫司汀、依托泊苷、阿糖胞苷、马法兰）方案在淋巴瘤的AHSCT预处理中较为常用。在干细胞回输上，应提前做好准备以避免出现细胞聚集现象，输注过程中还需加强临床质量控制管理，出现不良事件时应及时进行对症处理。植入后定期监测全血细胞计数等指标直至移植后100 d，以评估植入情况。移植后部分淋巴瘤亚型需行维持治疗以减少复发和治疗失败风险，提高生存率；针对不同淋巴瘤亚型，可采取不同的维持治疗方案，对于移植后复发高危患者，现已有BTK抑制剂、免疫调节剂等多种不同作用机制的新药上市，目前针对新药开展的疗效和安全性研究也在进一步探索中。淋巴瘤患者接受AHSCT治疗后造血恢复需要一定的时间，移植后应采取措施避免并发症的发生，植入成功后也应定期进行疗效评价及随访。对于适合移植的淋巴瘤患者，建议尽早转诊到移植中心行AHSCT治疗，以免延误最佳治疗时机。

［关键词］淋巴瘤；自体造血干细胞移植；临床实践

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Clinical practice optimization exploration and future prospects of autologous hematopoietic stem cell transplantation for lymphoma

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［**Abstract**］Autologous hematopoietic stem cell transplantation (AHSCT) is one of the effective treatments for highly aggressive and relapsed/refractory lymphoma, which can bring survival benefits to patients. In recent years, with the advent of new drugs such as small molecule targeted drugs, monoclonal antibodies, cell therapy and immunotherapy, more choices are provided for lymphoma patients, however, AHSCT still occupies an important position in the treatment of lymphoma. This paper summarized the indications

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eligible for AHSCT and its timing, and introduced the treatment process, post transplantation management and precautions of AHSCT in detail. The indications and timing of AHSCT are closely related to disease subtypes, risk stratification and disease status before transplantation. Before AHSCT, patients need to undergo pre-transplant induction and efficacy evaluation. The induction scheme varies according to different lymphoma subtypes, which can be selected according to the recommendations of corresponding guidelines. Currently the widely used clinical efficacy evaluation standard is imaging remission (CT /MRI evaluation) and metabolic remission (PET/CT evaluation). Every step of the AHSCT process is closely related to posttransplant outcome and prognosis. The overall process includes stem cell mobilization and collection, pretreatment prior to transplantation, stem cell reinfusion, comorbidity management and implantation evaluation. Formulating a good mobilization strategy to ensure the smooth development of transplantation is the most critical step. It is reasonable to choose stem cell mobilization regimen according to disease status after induction therapy, which is beneficial to improve mobilization success rate. Referring to the experience of hematopoietic stem cell mobilization abroad, steady-state mobilization is preferred in patients with stable disease, such as patients with CR1/CR2; in terms of stem cell collection, previous clinical experiences domestically and abroad mostly recommend that the optimal target collection of peripheral blood stem cells (PBSC) is 5×10^6 $CD34^+$ cells/kg. A recently published study suggests that a PBSC of 4.5×10^6-8×10^6 $CD34^+$ cells/kg in myeloma patients generates significantly better survival, and the optimal PBSC threshold for lymphoma patients needs further study. The evaluation of autograft is now evolving from only $CD34^+$ cells model, and studies have shown that autograft absolute lymphocyte count (A-ALC) can be introduced in autograft evaluation. Myeloablative pretreatment should be used before AHSCT, BEAM (carmustine, etoposide, cytarabine and melphalan) regimen is commonly used in AHSCT pretreatment of lymphoma. For stem cell reinfusion, preparations should be made in advance to avoid cell aggregation. Clinical quality control and management should be strengthened during infusion, and targeted treatment should be carried out in time in case of adverse events. After implantation, the complete blood count and other indicators were monitored regularly until 100 days after the transplantation to evaluate engraftment. After transplantation, patients with certain lymphoma subtypes need maintenance treatment to reduce the risk of recurrence and treatment failure, and to improve survival rate. Different maintenance treatment schemes can be adopted for different lymphoma subtypes. For patients at high risk of recurrence after transplantation, a variety of new drugs with different action mechanisms such as BTK inhibitors and immunomodulators have been launched into the market. At present, the research on the efficacy and safety of new drugs is also under further exploration. It takes a certain amount of time for lymphoma patients to get hematopoiesis recovery after AHSCT treatment. After transplantation, measures should be taken to avoid complications. After successful engraftment, curative effect evaluation and follow-up should be performed regularly. Lymphoma patients eligible for transplantion should be transferred to transplantion centers for AHSCT treatment at an early stage, to avoid missing the best AHSCT timing.

［**Key words**］ Lymphoma; Autologous hematopoietic stem cell transplantation; Clinical practice

淋巴瘤是一类异质性的淋巴恶性肿瘤，世界卫生组织将其分类为霍奇金淋巴瘤（Hodgkin lymphoma，HL）和非霍奇金淋巴瘤（non-Hodgkin lymphoma，NHL）。NHL发病率约占所有淋巴瘤的90%，常见的NHL亚型包括弥漫大B细胞淋巴瘤（diffuse large B-cell lymphoma，DLBCL）、滤泡性淋巴瘤（follicular lymphoma，FL）、外周T细胞淋巴瘤（peripheral T-cell lymphoma，PTCL）、套细胞淋巴瘤（mantle cell lymphoma，MCL）等[1-3]。自体造血干细胞移植（autologous hematopoietic stem cell transplantation，AHSCT）是高度侵袭性和复发/难治性淋巴瘤患者的有效治疗方式。2017年欧洲接受移植治疗的40 000例患者中，超过8 000例淋巴瘤患者接受AHSCT治疗[4]。2019年中国造血干细胞移植登记数量为12 323例，其中AHSCT为2 723例（22%），而HL和NHL分别占所有AHSCT患者的4%和41%[5]。我国自1989年中国医学科学院肿瘤医院内科完成第1例自体骨髓移植治疗恶性淋巴瘤至今已有30年的历史，技术发展较为成熟[6]。本文将对AHSCT适应证、治疗时机、治疗流程以及在移植后管理进行讨论。

1 AHSCT概述

美国移植和细胞治疗学会（American Society for Transplantation and Cellular Therapy，ASTCT）、美国国家综合癌症网络（National

Comprehensive Cancer Network，NCCN）、欧洲血液和骨髓移植学会（European Society for Blood and Marrow Transplantation, EBMT）指南以及中国临床肿瘤学会（Chinese Society of Clinical Oncology，CSCO）均推荐AHSCT用于部分侵袭性淋巴瘤亚型的一线巩固治疗和复发/难治性淋巴瘤的挽救性治疗[7-10]。AHSCT用于侵袭性NHL的一线巩固治疗可实现55%的5年无事件生存率（event-free survival，EFS）及74%的5年总生存率（overall survival，OS）[11]；其中国际预后指数（international prognostic index，IPI）高中危及高危的NHL患者接受AHSCT可显著延长无进展生存期（progression-free survival，PFS）[12]。利妥昔单抗联合化疗已发展为部分NHL患者的标准治疗，淋巴瘤治疗已迈进靶向新药时代。然而，研究[13]证实，即使是新药时代，AHSCT仍是NHL不可或缺的重要治疗手段。有研究发现，针对CHOP方案（环磷酰胺、阿霉素、长春新碱和泼尼松）或R-CHOP（CHOP联合利妥昔单抗）治疗后的高中危及高危NHL患者，AHSCT作为巩固治疗较对照组可显著改善高危患者的PFS（75% *vs* 41%，*P*=0.001）与OS（82% *vs* 64%，*P*=0.010）。同时，针对利妥昔单抗治疗失败的DLBCL患者，AHSCT仍有明显的疗效；早期和晚期利妥昔单抗治疗失败的3年PFS分别为44%和52%，3年OS分别为50%和67%。无论疾病复发的时间如何，AHSCT仍是复发/化疗敏感DLBCL的有效治疗选择[14]。近年来，随着一些新药的研发上市，AHSCT前诱导方案也在不断优化。一项前瞻性纳入190例MCL患者的研究[15]显示，BR方案（苯达莫司汀、利妥昔单抗）相比来源于回顾性对列的R-CHOP作为诱导治疗可为适合和不适合移植的MCL患者带来更长的PFS（3年PFS：66.0% *vs* 51.2%，*P*=0.003）；在适合移植的患者亚组分析中，3年PFS差异无统计学意义（82.2% *vs* 67.8%，*P*=0.220），表明针对适合移植的MCL患者，BR与R-CHOP同样有效。

AHSCT的适应证和治疗时机与疾病亚型、危险分层及移植前疾病状态紧密相关。对于一线巩固治疗的患者，AHSCT主要适用于年龄≤65岁的MCL患者、除间变性淋巴瘤激酶（anaplastic lymphoma kinase，ALK）阳性的间变性大细胞淋巴瘤（anaplastic large cell lymphoma，ALCL）外的PTCL以及高中危/高危DLBCL患者；对于复发/难治患者，AHSCT可作为挽救治疗敏感的淋巴瘤患者的解救性巩固治疗[16]。建议疾病完全缓解（complete response，CR）或至少部分缓解（partial response，PR）的患者行AHSCT。一项研究回顾性分析了570例经AHSCT治疗的PTCL患者的预后风险因素，结果显示，预后指数≥2（*P*<0.001）和部分缓解（*P*=0.041）均为影响移植后总生存期的重要危险因素[17]。多因素分析表明，移植前疾病状态与PTCL患者移植预后显著相关，CR患者较PR患者移植后的OS（81.0% *vs* 59.3%，HR=8.127，95% CI：1.851~35.673，*P*=0.006）与PFS（71.8% *vs* 17.8%，HR=4.978，95% CI：1.565~15.838，*P*=0.007）更优[18]。

2 AHSCT流程

AHSCT整体治疗流程包括干细胞动员及采集、移植前预处理、干细胞回输、合并症管理、植入情况评估。此外，在行AHSCT前，需要对患者进行移植前诱导及疗效评估（图1）。

2.1 移植前诱导

2.1.1 诱导治疗方案

淋巴瘤患者的诱导治疗方案常以化疗为主。针对适合AHSCT一线巩固治疗的患者，应根据其病理学类型和危险度分层，选择相应的一线诱导治疗方案。针对复发或难治患者的挽救性巩固治疗，理想的挽救治疗方案应兼具高治疗反应率、可接受的毒性以及对造血干细胞损害较小的特点，需要结合患者的一线治疗反应与耐受性、缓解持续时间、复发时的疾病特征与预后、患者年龄等进行选择[16]。具体诱导方案根据淋巴瘤

亚型不同有所差异，可参考NCCN以及CSCO指南具体推荐进行选择。

2.1.2 疗效评价

当前研究及临床实践提示疾病应达到CR或至少PR的患者行AHSCT[7, 9, 16, 18]。2014年Lugano会议最新修订的疗效评价标准是目前临床中广泛使用的疗效评价标准，分为影像学缓解（CT/MRI评价）和代谢缓解（PET/CT评价）[19]。

2.2 干细胞动员和采集

2.2.1 干细胞动员

传统的外周血干细胞（peripheral blood stem cells，PBSC）动员方案包括单独采用粒细胞集落刺激因子（granulocyte-colony stimulating factor，G-CSF）稳态动员和G-CSF联合化疗动员的非稳态动员[20]。CR患者适用于稳态动员，非稳态动员方案的选择则基于患者的疾病特征和临床实践指南，多主张应用疾病特异性化疗动员方案，以尽可能避免额外化疗周期的负担，同时有效动员造血干细胞[21]。

2014年ASTCT专家共识推荐G-CSF单药稳态动员作为一线首选方案，其动员动力学可预测，允许可预期的干细胞采集和科室工作安排，但失败率高达38%[22]。新一代造血干细胞动员剂普乐沙福是CXC族趋化因子受体4（CXCR4）拮抗剂，CXCR4在造血和非造血细胞上均广泛表达，CXCL2（SDF-1）/CXCR4轴参与体内T淋巴细胞的迁移和归巢（包括骨髓）、造血、免疫调节和发育[23]。普乐沙福可阻断CXCL2（SDF-1）/CXCR4的相互作用与信号转导，并协同下

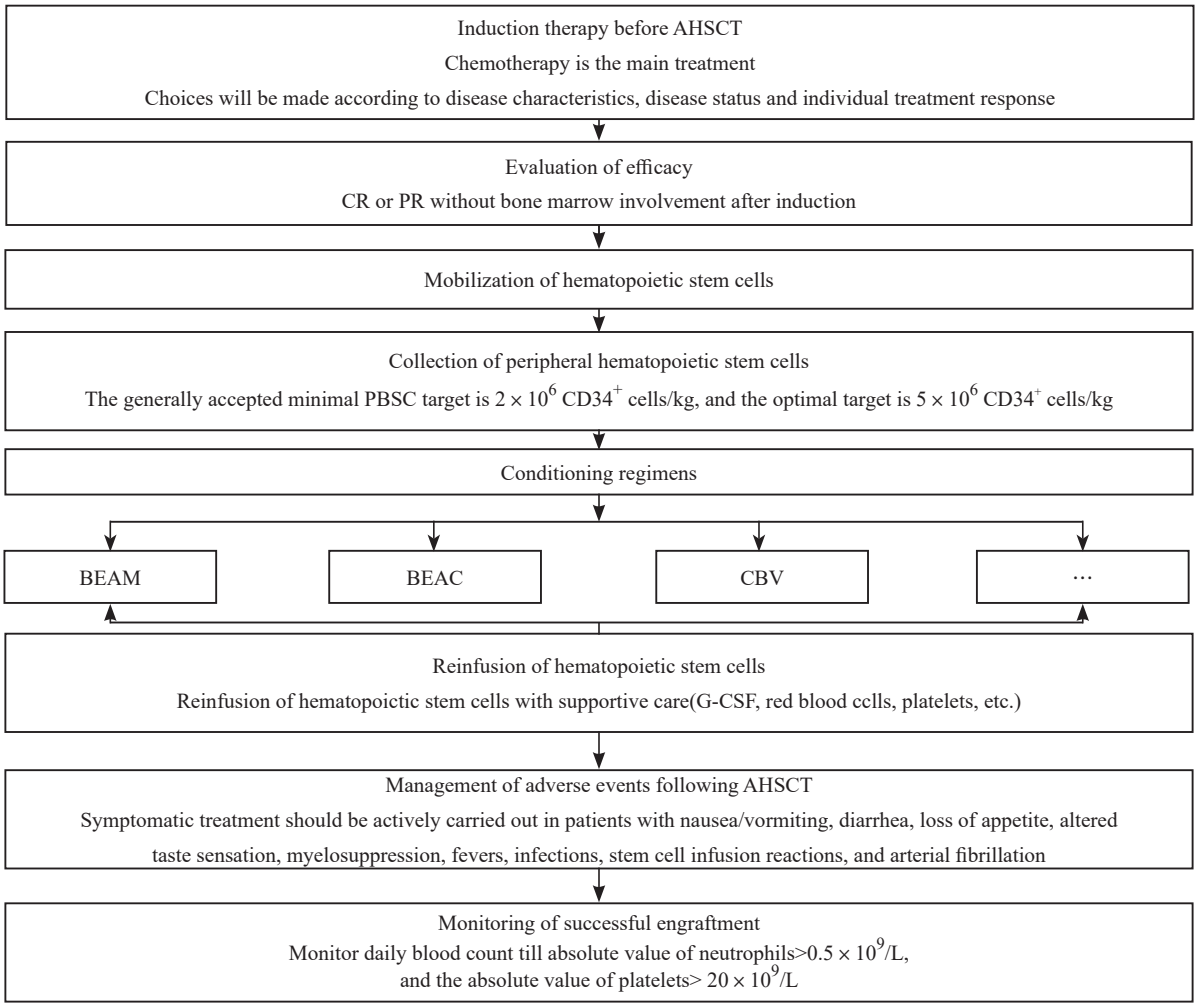

图 1 AHSCT流程

Fig. 1 Process of AHSCT

调黏附分子表达，导致骨髓微环境中高表达的CXCL12（SDF-1）对造血干细胞失去趋化性，造血干细胞无法按CXCL12（SDF-1）浓度梯度进行跨内皮移行并迁移至骨髓龛，从而动员骨髓造血干细胞进入外周血循环[24]。全球NHL多中心Ⅲ期研究[25]以及中国NHL Ⅲ期研究[26]结果均显示，相比G-CSF联合安慰剂，G-CSF联合普乐沙福动员可显著提高动员成功率（即≤4个采集日内采集≥2×10^6个细胞/kg的患者比例；全球：47.3% *vs* 86.7%，*P*<0.001；中国：66.0% *vs* 88.0%，*P*=0.009）及优质动员成功率（即≤4个采集日内采集≥5×10^6个细胞/kg的患者比例；全球：19.6% *vs* 59.3%，*P*<0.001；中国：20.0% *vs* 62.0%，*P*=0.009）。虽然对照化疗动员的疗效暂无前瞻性随机研究的数据支持，但已有的非随机研究数据显示，其相比化疗动员疗效相似或可提高干细胞采集量、降低动员失败率[27-29]。因此，普乐沙福联合G-CSF一线稳态动员推荐适用于以下情况：目标是采集到尽可能多的$CD34^+$细胞；实时PB $CD34^+$计数不可获得；或优先考虑在尽可能少的采集次数内获得足够的$CD34^+$细胞[25]。此外，国外单中心经验提示，在首次动员时存在高危因素的患者，如年龄>60岁、既往接受≥三线化疗、既往接受干细胞毒性药物（包括嘌呤类似物、来那度胺、马法兰等）治疗等，建议采用G-CSF联合普乐沙福的一线稳态动员，以提高动员成功率[30]。在选择G-CSF单药或联合化疗进行动员时，建议监测PB $CD34^+$“按需”使用普乐沙福，可有效地预防动员失败[25]。

美国梅奥诊所临床实践[31]经验主要参考疾病状态进行动员方案的选择。针对疾病稳定的患者，首选G-CSF单药稳态动员，根据第4天PB $CD34^+$计数按需使用普乐沙福并于第5天进行干细胞采集；针对活动性复发的患者，采用R-ICE（利妥昔单抗、异环磷酰胺、卡铂、依托泊苷）、R-DHAP（利妥昔单抗、顺铂、阿糖胞苷、地塞米松）等联合G-CSF进行挽救性化疗动员，当白细胞计数（white blood cell，WBC）恢复后＞1.0×10^9/L时，监测PB $CD34^+$细胞数。若连续3天PB $CD34^+$细胞数＜10/μL，应联合普乐沙福进行治疗。

参考国外目前的造血干细胞动员经验，建议采取图2的路径进行造血干细胞动员。在疾病稳定状态下，例如达到CR1/CR2的患者，建议优选稳态动员。与非稳态动员相比，稳态动员的主要优势包括可预测干细胞采集时间、毒性相对较低、减少周末采集、提高科室资源利用效率，并缩短动员至移植时间。单用G-CSF稳态动员干细胞采集量低，动员失败风险高[32]，而G-CSF联合普乐沙福动员不仅可维持稳态动员的优势，同时可提高动员成功率。

对于活动性复发的患者，建议优选疾病特异性的非稳态动员，通常选择挽救治疗中敏感的化疗方案，如R-ICE、R-DHAP等。化疗动员可在有限的单采次数内增加$CD34^+$细胞采集量，并可能具有一定的抗肿瘤活性[33]。诊断为NHL本身是动员不佳的高危因素[34]，普乐沙福用于化疗动员不良的NHL患者可显著提高动员成功率及$CD34^+$细胞采集量，使大多数动员不良的患者有效地采集造血干细胞[35-36]。2019年EBMT手册建议化疗动员时需在采集前每日监测PB $CD34^+$，以准确判断PB $CD34^+$峰值及单采的最佳时机[32]。对于不包含普乐沙福的动员方案，在动员过程中应监测采集前PB $CD34^+$计数，若PB $CD34^+$计数＜10/μL，推荐立即给予普乐沙福抢先干预；若PB $CD34^+$计数介于（10~20）/μL，需结合动员不良的影响、计划移植次数、所需细胞总量综合考虑是否联合普乐沙福治疗[21]。普乐沙福抢先干预可有效提高$CD34^+$细胞数量和动员成功率[37]，且更具有成本效益。此外，还可根据当日采集量决定是否联合普乐沙福，若第1天干细胞采集量<1.5×10^6个$CD34^+$细胞/kg或第1天后采集量<0.5×10^6个$CD34^+$细胞/kg，应联合普乐沙福治疗[31]。

2.2.2 干细胞采集和冻存

国内外临床经验[21, 38]推PBSC的最佳目标采集量为5×10^6 $CD34^+$细胞/kg，单次移植的最

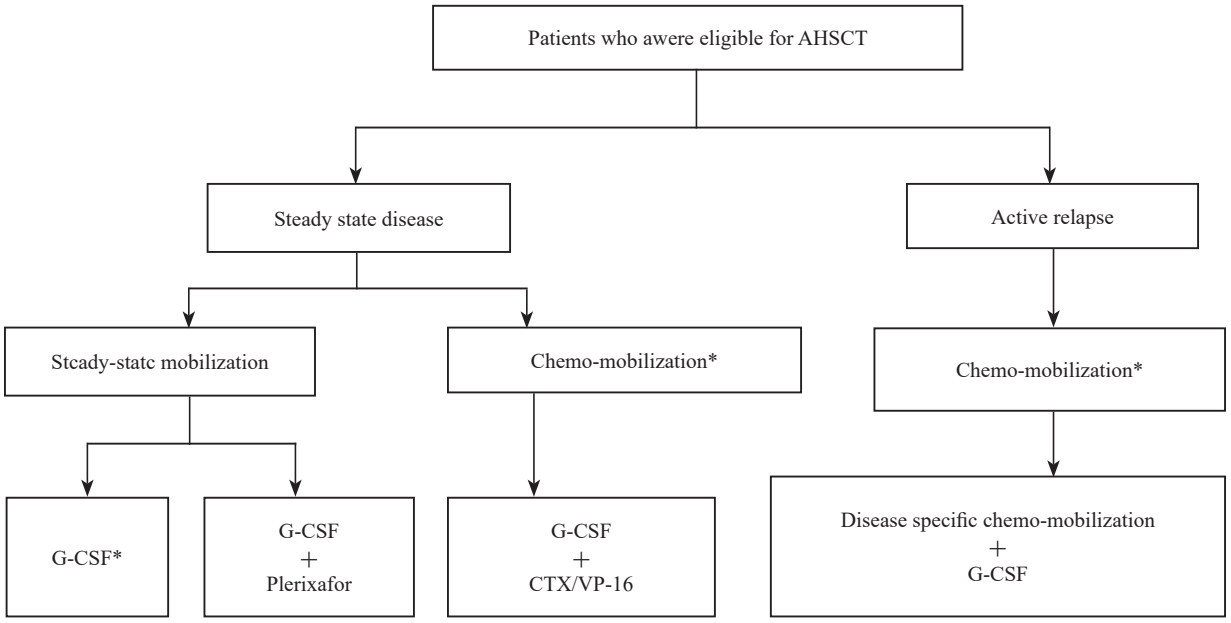

图 2 PBSC干细胞动员路径

Fig. 2 Mobilization algorithm of PBSC

*: For PBSC mobilization with G-CSF alone or in combination with chemotherapy, the introduction of plerixafor are recommended as rescue treatment in the following situations: ① PB $CD34^+$ cell count prior to apheresis<10/μL, pre-emptive plerixafor; ② pre-apheresis PB $CD34^+$ cell count between10-20/μL, consider whether to use plerixafor based on the impact of poor mobilization, planned number of transplants and total amount of stem cells required (if day 1 yield<1.5×10^6 $CD34^+$/kg add plerixafor; if yield beyond day 1<0.5×10^6 $CD34^+$/kg add plerixafor).

小安全目标采集量是2×10^6 $CD34^+$细胞/kg，更高的采集目标与快速植入和更优的长期生存相关。2021年美国血液学会（American Society of Hematology，ASH）会议上的一项回顾性研究显示，在骨髓瘤患者中，PBSC 4.5×10^6~8×10^6个$CD34^+$细胞/kg相比≤4.5×10^6和≥8×10^6个$CD34^+$细胞/kg的患者中位PFS和OS均显著延长（P=0.001，P=0.029），针对淋巴瘤患者推荐的PBSC最佳阈值还有待进一步研究[39]。自体移植物的评价不仅限于$CD34^+$细胞，鉴于自体移植绝对淋巴细胞计数（autograft absolute lymphocyte count，A-ALC）0.5109/kg的患者PFS和OS均有显著延长的趋势，梅奥医学中心将A-ALC也纳入到自体移植物评估中[40]。通过PB $CD34^+$计数检测判断采集时机，当$CD34^+$计数≥20/μL的第1天，即可进行造血干细胞采集。干细胞采集过程中，应密切监测电解质和凝血参数[41]，确保干细胞采集过程顺利进行。

此外，采集目标应与需要采集的次数平衡，若计划多次AHSCT，应采集更多数量的造血干细胞保存[16]。对于造血干细胞的冻存，美国细胞疗法认证委员会（The Foundation for the Accreditation of Cellular Therapy and NetCord，NetCord-FACT）标准要求存储温度低于−150 ℃。最常用浓度10%的二甲基亚砜（dimethyl sulfoxide，DMSO）为低温保护剂[42]。通常将干细胞保存在−160 ℃~−180 ℃的液氮中，此前采用可控速率的机械冷冻机将冷冻速率由−1 ℃/min~−2 ℃/min缓慢冷却至−40 ℃~−50 ℃，然后以−5 ℃/min~−10 ℃/min冷却至−80 ℃~−90 ℃。此时可选择将干细胞转移到液氮中进行存储，也可继续在冷冻机中以受控的速度冷冻，直到温度达到液氮温度。此外，临床实践中为节约成本，也可采用浓度低于10%的DMSO以及不可控速率的机械冷冻机−80 ℃储存，但应尽可能避免长期储存[43]。冻结装置必须平衡产品与冻结室内环境之间的温度差，评估低温贮藏温度的范围，同时进行监控并记录[44]。

2.3 移植前预处理

AHSCT应采用清髓性预处理方案，常用于

淋巴瘤AHSCT预处理的方案包括BEAM（卡莫司汀、依托泊苷、阿糖胞苷、马法兰）、BEAC（卡莫司汀、依托泊苷、阿糖胞苷、环磷酰胺）、CBV（环磷酰胺、卡莫司汀、依托泊苷）和包含全身放疗的方案等[16]。

目前国内外仍缺乏关于清髓性预处理方案疗效和毒性的大样本随机对照研究，因经典的BEAM预处理方案具有一定的疗效，耐受性尚可，故在临床上最为常用。具体方案：将外周血干细胞输注第1天定为0 d，在第2~4天静脉滴注依托泊苷800 mg/(m^2·d)1次/12 h，阿糖胞苷1 600 mg/(m^2·d)1次/12 h。第5天静脉滴注卡莫司汀300 mg/m^2。第6天口服马法兰140~160 mg/m^2[44-45]。目前国内仅上市了马法兰注射剂，尚无比较口服与注射马法兰作为淋巴瘤患者AHSCT预处理方案的研究，但有研究比较了口服或静脉注射马法兰联合卡莫司汀、依托泊苷作为多发性骨髓瘤患者AHSCT预处理方案的效果。口服或注射马法兰两组采集的$CD34^+$细胞剂量，中性粒细胞和血小板重建，以及感染发生率差异无统计学意义；与口服马法兰相比，注射马法兰的患者3~4级口腔黏膜炎有增加趋势，但差异无统计学意义（28.5% *vs* 38.5%，*P*=0.100）；两组的无病生存期（disease-free survival，DFS）和OS差异无统计学意义（25个月 *vs* 38个月，*P*=0.600），但对于疾病缓解期（CR、VGPR或PR）行AHSCT的患者，静脉注射马法兰的DFS和OS更优（25个月 *vs* 未达到，*P*<0.050；36个月 *vs* 未达到，*P*<0.005）[46]。

此外，由于国内卡莫司汀来源受限，因此所有包含该药物的预处理的应用受到极大限制。近期有研究[47]发现，联合司莫司汀的改良BuCy方案（司莫司汀＋阿糖胞苷＋白消安＋环磷酰胺）和SEAM方案（司莫司汀＋依托泊苷＋阿糖胞苷＋美法仑）有较好的疗效。改良BuCy方案与SEAM方案的2年FPS率分别为79%和70%（*P*=0.378）、OS率分别为81.0%和78.0%（*P*=0.789）；其中，与SEAM相比，改良的BuCy方案淋巴瘤患者造血重建时间略早，不良反应方面黏膜炎及腹泻发生率较低。

2.4 移植步骤：干细胞回输

干细胞回输是移植过程中的重要环节。移植中心应提前与干细胞冻存部门进行联系，明确干细胞解冻方案，并做好准备工作。准备就绪后，将干细胞解冻，并检测解冻后细胞活力和效力[42]，重新计算输入的造血干细胞数量，在预处理方案治疗结束后48 h内完成对外周血干细胞的回输治疗，避免因输注时间推迟出现细胞聚集现象[48]。

整个输注过程中，应加强对临床质量控制的管理，如提前备好急救设备和常用急救药品；要求熟悉干细胞输注不良反应的护士进行陪同；保证有熟悉干细胞输注反应的医生和护士管理输注工作；输注前应检查患者的血压、脉搏、呼吸、体温等各项生命体征。每袋干细胞输注时，应每30 min检查一次血压和脉搏，一直到完成干细胞输注后2 h；如果每天输注造血干细胞后尿量2~3 mL/（kg·h），超过患者体重的10%，需要分为2次或者分为2 d以上进行；完成输注后，应采用生理盐水冲洗静脉管，以2倍维持量的速率输注5 h，同时检测患者各项生命体征等。输注后第5天给予重组G-CSF 5~10 μg/kg·d，直到连续2 d外周血WBC≥1.0×10^9/L。并给予患者红细胞和血小板输血治疗[49]。

2.5 不良事件管理

根据临床经验，对不良事件的管理给出如下建议[50-52]，见表1。

2.6 植入情况监测

植入成功标准参考每日全血细胞计数，中性粒细胞绝对值＞0.5×10^9/L，血小板绝对值＞20×10^9/L，持续5 d，后续至少1~2周检查1次，直至移植后100 d[44]。

3 移植后管理及注意事项

3.1 移植后维持治疗

AHSCT后有效的维持治疗有助于减少复发和治疗失败风险，提高生存率，但因淋巴瘤

亚型众多，不同亚型的维持治疗方案和周期不同，目前对最佳的维持治疗方案和周期尚不明确。基于现有的临床经验，Kanate等[53]综合分析了来自ASTCT、国际血液与骨髓移植研究中心（Center for International Blood and Marrow Transplant Research，CIBMTR）以及EMBT的26位权威专家关于AHSCT后维持治疗的推荐及建议，提出经典HL患者推荐布伦妥昔单抗维多汀（brentuximab vidotin，BV）维持治疗；MCL、FL患者推荐利妥昔单抗维持治疗；而DLBCL患者不推荐维持治疗。此外，针对移植后复发高危患者，多个不同作用机制的新药已上市，如BTK抑制剂伊布替尼、免疫调节剂来那度胺、蛋白酶抑制剂硼替佐米以及化疗联合免疫治疗药物[54]，目前正在开展临床研究正着手探索这些新药维持治疗的疗效和安全性。

3.2 移植后监测与随访

淋巴瘤患者接受AHSCT治疗后，造血恢复需要2~3周，应接受重组造血生长因子输注，帮助缩短严重中性粒细胞减少时间；此外，红细胞和血小板输注对于预防或治疗长时间的血细胞减少症状及其并发症至关重要。待植入成功，术后2~3个月进行疗效评价，并酌情进行病史、体格检查、实验室评估、影像学/核医学成像和骨髓活检等相关检查，针对病情无复发的患者，按淋巴瘤诊疗常规进行随访[51]。所有AHSCT术后患者应保持健康积极的生活方式，预防慢性疾病，同时，移植中心应为AHSCT术后患者提供相关的教育或咨询服务[55]。

表 1 AHSCT不良反应及其管理

Tab. 1 Management of adverse events following AHSCT

Adverse events	Management strategies
Nausea/vomiting	Antiemetics
Diarrhea	Antidiarrheals and fluids to prevent dehydration
Loss of appetite	Dexamethasone to stimulate appetite
Altered taste sensation	Zinc tablets or lemon candy
Mucositis	Pelifermin, anesthetic mouth wash, supersaturated calcium phosphate oral rinse, opioid analgesic, parenteral nutrition in severe case
Myelosuppression	G-CSF, blood component transfusions
Fevers	Evaluate for infections, antipyretics
Fatigue	Exercise
Infections (bacterial, viral, fungal, etc.)	Symptomatic and supportive care as appropriate based on etiological analysis with reference to international guidelines. For patients with pneumocystis jiroveci pneumonia, recommend dapsone 50 mg and atovaquone 750 mg orally daily as 2 divided doses
Clostridium difficile diarrhea	Hand washing/metronidazole, oral vancomycin
Hemorrhagic cystitis	Mesna for prophylaxi
Cataracts	Topical corticosteroids or emollients
Parotitis	Chewing gums, lemon drops
Infertility	Sperm or oocyte cryopreservation
Hypothyroidism/osteoporosis	Avoid TBI
Flushing/hypotension/breath odor due to DMSO/allergic reactions/ chest tightness/dyspnea	Slow down infusion rate or give acetaminophen, histamine blockers, corticosteroids
Atrial fibrillation	Beta-blockers and calcium channel blockers should be used for rhythm management; anticoagulation therapy to prevent stroke and potential risk factors management

4 总结与展望

AHSCT在侵袭性及难治/复发的淋巴瘤治疗中具有重要价值，尤其是在改善患者生存中起到关键作用，对于具备移植指征的患者早期转诊至移植中心行AHSCT治疗可改善预后。移植流程中的每个环节都与移植预后紧密相关。虽然当前AHSCT技术已获得长足的发展，但未来仍需进一步研究，对移植过程中各环节进行优化，从而进一步改善患者生存和生活质量。对于目前开展的一系列AHSCT联合新药或新的治疗方法的探索性研究，有望为淋巴瘤的治疗带来革命性的进步。

利益冲突声明：所有作者均不存在利益冲突。

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