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微小残留病在多发性骨髓瘤中的应用进展与临床争议

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摘　要

多发性骨髓瘤(multiple myeloma, MM)是骨髓内浆细胞异常增生所致的血液系统恶性肿瘤，具有异质性强、易复发等特点。随着多种新型药物的出现及治疗技术的更新，多数MM患者可获得临床缓解；但常规检测难以发现体内残存微量肿瘤细胞，即微小残留病(minimal residual disease, MRD)，而MRD正是导致复发的根源。近年来MRD在MM中的价值逐渐突显，但同时也存在诸多争议亟待解决。本文结合近年来国内外相关研究，系统综述MRD在MM中的实际价值并深入剖析当前存在的主要争议，探讨未来研究方向，为实现MM个体化精准治疗提供参考。

关键词

多发性骨髓瘤，微小残留病，检测技术，临床应用

Advances and Clinical Controversies in the Application of Minimal Residual Disease in Multiple Myeloma

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Abstract

Multiple myeloma (MM) is a hematologic malignancy characterized by abnormal proliferation of plasma cells in the bone marrow, with prominent features of high heterogeneity and frequent relapse.

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With the emergence of various novel agents and advances in therapeutic techniques, most patients with MM can achieve clinical remission. However, conventional detection methods fail to identify minimal residual tumor cells, namely minimal residual disease (MRD), which is the root cause of disease relapse. In recent years, the clinical value of MRD in MM has become increasingly evident, yet numerous controversies remain to be addressed. This article systematically reviews the practical value of MRD in MM based on recent domestic and international studies, deeply analyzes the major current controversies, and explores future research directions, aiming to provide a reference for the implementation of individualized precision therapy in MM.

Keywords

Multiple Myeloma, Minimally Residual Disease, Detection Techniques, Clinical Applications

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1. 引言

作为一种起源于浆细胞的恶性克隆性疾病，多发性骨髓瘤(multiple myeloma, MM)的主要特征为骨髓中异常浆细胞大量增殖，分泌单克隆免疫球蛋白(monoclonal immunoglobulin, MI)并侵犯骨骼、血液系统、肾脏等多个器官，引起骨骼损伤、肾功能不全、贫血、钙代谢异常等多种临床表现[1] [2]。数据表明 MM 约占血液系统肿瘤 10%，国内年龄标化发病率约 1/10 万人，年龄标化死亡率约 0.67/10 万人，高发年龄为 55~65 岁，男女发病比例约 2.35:1 [3]。

近年来，随着医疗水平改善，MM 诊疗模式逐渐从传统的以化疗为主逐渐转向以新型药物为主的个体化治疗(personalized treatment, PT)模式[4]；数据表明药物联合治疗有效率可达 80%~95%，完全缓解(complete remission, CR)率为 15%~50%，同时患者中位生存期(median survival time, MST)明显延长[5]；但需要警惕的是复发仍旧是临床的主要难题——CR 患者 5 年复发率超过 80%，其根源在于体内存在微小残留病(minimal residual disease, MRD) [6]。MRD 指的是肿瘤患者经过积极治疗后体内残存的少量具有增殖能力的肿瘤细胞，常规形态学检测无法测出但可通过高灵敏检测技术发现。近年来许多学者逐渐重视 MRD：2016 年国际骨髓瘤工作组(international myeloma working group, IMWG)将 MRD 治疗标准纳入 MM 诊疗指南，2017 年国家综合癌症网络(national comprehensive cancer network, NCCN)及中国 MM 诊疗指南均将 MRD 阴性和持续 MRD 阴性作为疗效判定标准与最佳疗效指标[7] [8]。同时近年来 MRD 检测技术日新月异使得其在 MM 诊疗中地位日益凸显，但在检测技术选择、数据解读、临床应用、疗效评估等诸多方面争议颇多，尚未形成统一规范。本文旨在对 MRD 在 MM 的应用进展及临床争议进行系统梳理，为临床实验提供参考。

2. MRD 相关概念与检测技术进展

2.1. 相关概念

当下关于 MM 相关 MRD 定义为：患者经诱导治疗、巩固治疗或造血干细胞移植治疗后骨髓或外周血液中残存的、具有克隆性增殖能力的异常浆细胞，其数量低于常规形态学检测限(limit of detection, LOD)，对于 MM 而言意味着异常浆细胞比例低于 5%；但可通过高灵敏检测技术识别[9]。较之常规形态学检测，MRD 能更精准反映患者体内肿瘤负荷，是治疗方案决策、疗效评估、疾病复发预测的重要指标[10]。但

需要警惕的是 MRD 阴性或者持续阴性并不意味着疾病治愈，这只意味着当下检测技术尚未发现可检测到的肿瘤细胞，而实际上患者体内仍可能存在微量的肿瘤细胞或骨髓外微小病灶，一旦这些病灶因患者免疫功能受损等因素再次增殖，仍可能导致 MM 复发[11]。

2.2. 主要检测技术及进展

当下 MM 相关 MRD 检测技术主要分为两类：基于细胞水平的检测技术与基于分子水平的检测技术；经过多年不断发展两类技术互补；其中二代流式细胞术(next-generation flow cytometry, NGF) [12]与二代测序[13] (next-generation sequencing, NGS)已逐渐成为临床主流检测技术。

2.2.1. 基于细胞水平的检测技术

该技术核心为通过免疫表型差异实现定量分析，多参数流式细胞术(multi-parameter flow cytometry, MFC)及 NGF 为当下主流技术[14]。MFC 采用 4~6 色抗体组合，灵敏度可达 10^{-4}~10^{-5}，具有快速、低成本、无需基线样本等优势[15]。NGF 则指 8 色以上的高灵敏技术，灵敏度高达 10^{-5}~10^{-6}；最常用为 CD38/CD138/CD45 联合 CD19、CD56 的“骨架”抗体组合通过细胞轻链差异区分克隆[16]。两种技术共同局限在于受实验流程、操作技术影响大，且达雷托尤单抗治疗会干扰 CD38 识别进而导致假阴性，因此限制其临床应用[17]。

2.2.2. 基于分子水平的检测技术

分子水平技术核心在于依赖基因特征而实现检测，包括 NGS、实时荧光定量聚合酶链反应(real-time quantitative polymerase chain reaction, qRT-PCR)以及核糖核酸测序(RNA sequencing, RNA-seq) [18]-[20]。NGS 通过测序免疫球蛋白重排片段其灵敏度可达 10^{-5}~10^{-6}，适用率超 90%，可解析克隆演化且易于标准化，但缺点是成本高、周期长且依赖基线样本[21]。qRT-PCR 早期应用灵敏度较前者相当，同时需个性化引物，且易因基因重排异常漏检而逐渐被 NGS 取代[22]。新兴技术 RNA-seq 利用基因高表达特异性可避免体细胞突变干扰，在灵敏度不受影响前提下还能提供全转录组信息，同时准确性更高，但劣势在于成本与复杂度高，目前尚处于临床验证阶段[23]。

2.2.3. 其他检测技术

作为 qRT-PCR 的升级版，数字 PCR (digital PCR, dPCR)通过单分子定量检测其灵敏度高达 10^{-6}~10^{-7}，且特异性高，但受限于成本与操作门槛[24]。正电子发射计算机断层显像(positron emission tomography-computed tomography, PET-CT)目前主要应用于骨髓外 MRD 病灶的监测，但受限于灵敏度、辐射与高成本，目前只作为补充检测手段[25]。

3. 临床应用进展

伴随对 MRD 检测技术不断成熟，其在 MM 的临床应用价值逐渐加深、应用日益广泛，已逐渐成为 MM 精准诊疗核心指标之一。当下主要用于疗效评估、预后判断、治疗方案调整及监测复发等多方面。

3.1. 疗效评估

基于骨髓形态学、血清 M 蛋白等指标的传统 MM 疗效评估将患者分为 CR、非常好的部分缓解(very good partial response, VGPR)等，但其缺点在于不能区分 CR 患者体内是否存在 MRD，也就不能对患者复发风险进行准确评估[26] [27]。当下 IMWG 等权威机构已将 MRD 监测纳入疗效评估体系，提出“MRD 阴性的完全缓解(CR-MRD$^-$)”标准，即 CR 同时 MRD 检测也为阴性(灵敏度 $\geq 10^{-5}$)，此类患者复发风险更低、生存周期更长[28]。另外 MRD 检测可对不同治疗方案疗效进行评估，其动态水平变化可及时反应

疗效，临床可根据其水平变化及时调整治疗方案。

3.2. 预后判断

作为 MM 患者预后的独立预测因子，MRD 结果与无进展生存期(progression-free survival, PFS)、总生存期(overall survival, OS)等密切相关[29]。数据表明 MRD 阴性尤其是持续阴性患者预后、中位 PFS 明显优于阳性患者，而与是否移植、有无高危遗传学因素等关联不大[30] [31]。快速下降至阴性且阴性持续时间超过 12 月患者预后最佳，而水平下降缓慢或阴转阳则提示复发风险高；这是根据其动态变化水平进行预测判断[32]。另外，对于伴有高危细胞遗传学异常患者，MRD 可实现风险分层并识别不同亚群。

3.3. 治疗方案调整

如何指导个体化治疗是 MRD 检测的核心价值，过度治疗或治疗不足都是需要尽力避免的；这体现在巩固、维持与复发后治疗等不同阶段[33]。在巩固治疗阶段，CR 但 MRD 阳性患者需要强化治疗而 MRD 阴性则可减少治疗强度与时间[34]。维持治疗阶段自体造血干细胞移植(autologous stem cell transplantation, ASCT)后 MRD 阴性可缩短维持治疗时长而 MRD 阳性则需要延长治疗时长或更换药物，另外 MRD 阴转阳需启动挽救治疗措施[35] [36]。对于复发后治疗阶段，MRD 阴性提示挽救治疗有效但 MRD 阳性或水平升高则需要及时更换治疗方案[37]。

3.4. 复发监测

研究表明 MRD 是当前 MM 缓解后提示患者是否复发最敏感指标，较之临床症状的出现能提前数月检测到肿瘤细胞增殖进而实现早期预警[38]。MRD 阳性、水平持续升高是提示复发的重要信号，及时干预能明显延缓病程进展、提高生存质量、延长生存期。

4. 临床争议

尽管越来越多研究表明 MRD 在 MM 中临床应用价值重大，但仍需要面对检测技术标准化、数据解读、临床应用边界等多方面的争议，需进一步通过临床研究达成共识。

4.1. 检测技术标准化

缺乏统一规范使得其成为当下最主要争议之一。一方面是检测技术选择缺乏统一标准：作为主流技术的 NGF 与 NGS 各有优劣，对于初诊未留基线样标本患者仅能选择 NGF，但免疫表型不典型者 NGS 更准确，同时由于基层医疗机构缺乏 NGS 检测能力，这就导致检测结果缺乏可比性[39]。另一方面是操作与质控的缺乏统一标准，NGF 的抗体组合、圈门策略不同，NGS 样本处理、测序深度等环节受不同检测中心差异大[40]。再者检测样本选择不同也会干扰检测结果，例如骨髓标本有创性与取样误差、髓外 MRD 检测尚无统一标准，而 PET-CT 等手段也存在明显局限性[41]。

4.2. 解读标准缺乏统一

这主要体现在以下方面。首先，MRD 阴性定义与阈值不统一，IMWG 推荐灵敏度为$\geq 10^{-5}$，但高危患者是否需要更高灵敏度以及介于 10^{-6}~10^{-5} 之间患者如何干预尚无共识[42]。其次，对“持续阴性”时长(6 个月或 12 个月)以及阴转阳后临床意义缺乏统一标准[43]。第三，如何鉴别假阳性与假阴性也缺乏统一规范[44]。

4.3. 临床应用边界

当前研究对 MRD 应用边界也缺乏统一标准。第一，能否将 MRD 作为治疗终止指标，低危患者 MRD

持续阴性 ≥2 年后是否能终止维持治疗，高危患者是否需要延长维持治疗时间，目前缺乏数据支撑[45]。第二，MRD 对不同人群应用价值存在争议，例如其对于低危、老年患者及冒烟型多发性骨髓瘤(smoldering multiple myeloma, SMM)的价值目前尚未达成共识[46]。第三，如何将 MRD 与细胞遗传学、β2-微球蛋白等指标联合应用是否能提高预后判断准确性，也缺乏统一规范[47]。

5. 总结与展望

作为 MM 复发的根源，MRD 检测技术的更新迭代推动了 MM 的精准治疗；各种检测技术如 NGF、NGS 在疗效评估、预后判断等多方面发挥了重要作用；同时 CR-MRD 阴性成为对 MM 的临床治疗目标，进而实现可调控的精准治疗。但 MRD 在 MM 中的应用仍存在许多争议；这也就意味着未来需要建立多中心大样本研究，统一规范，明确应用边界，优化检测技术、降低成本等。另一方面，随着人工智能等新型技术的崛起更有助于个体化精准诊疗模型的探索，包括 MRD 阳性患者新型治疗策略、检测规范化、精准诊疗等，进而真正改善患者获益。

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