Advances in Clinical Medicine 临床医学进展, 2022, 12(1), 376-380
Published Online January 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.121057

Hans汉斯

急性单核细胞白血病迭患多发性骨髓瘤一例并文献复习

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收稿日期：2021年12月18日；录用日期：2022年1月7日；发布日期：2022年1月25日

摘　要

目的：探讨急性髓系白血病迭患多发性骨髓瘤的发生机制、治疗方法及预后。方法：对1例急性单核细胞白血病迭患多发性骨髓瘤患者的病例资料进行分析，并复习相关文献。结果：该例患者行小剂量地西他滨 + 阿克拉霉素 + VRd方案化疗2疗程，小剂量地西他滨 + CAG + 硼替佐米方案化疗1疗程，最终因原发病进展合并严重感染死亡，生存期10个月。结论：此类病例临床罕见，预后差，临床多为个案报道，目前治疗方案仍不能治愈大多数患者，化疗序贯移植或联合新的靶向药物有望延长患者生存期，改善预后。

关键词

多发性骨髓瘤，急性白血病，BCL-2，Venetoclax

Simultaneous Occurrence of Acute Myeloid Leukemia and Multiple Myeloma: A Case Report and Literature Review

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Received: Dec. 18th, 2021; accepted: Jan. 7th, 2022; published: Jan. 25th, 2022

Abstract

Objective: To investigate the pathogenesis, treatment and prognosis of simultaneous occurrence

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文章引用: 李智慧, 李丽, 王彦丽. 急性单核细胞白血病迭患多发性骨髓瘤一例并文献复习[J]. 临床医学进展, 2022, 12(1): 376-380. DOI: 10.12677/acm.2022.121057

of acute myeloid leukemia and multiple myeloma. Methods: The case data of a patient with acute monocytic leukemia complicated with multiple myeloma were analyzed and the related literatures were reviewed. Result: The patient was treated with low dose of decitabine + aclacinomycin + VRd for two courses of chemotherapy, low dose of decitabine + aclacinomycin + bortezomib for one course of chemotherapy. Finally, he died of progression of primary disease with severe infection and survived for 10 months. Conclusion: Such cases are rare in clinic and poor in prognosis, but most of them are reported in individual cases. At present, the treatment scheme cannot cure most patients. Sequential transplantation of chemotherapy or combined with new targeted drugs is expected to prolong the survival time of patients and improve the prognosis.

Keywords

Multiple Myeloma, Acute Leukemia, BCL-2, Venetoclax

1. 前言

急性髓系白血病(Acute myeloid leukemia, AML)是起源于造血干细胞的恶性克隆性疾病，以贫血、出血、感染、浸润为主要临床表现。多发性骨髓瘤(Multiple myeloma, MM)是一种恶性克隆性浆细胞疾病，以贫血、溶骨性骨质破坏、高钙血症、肾功能不全为主要特征。文献报道的大多为 MM 治疗后继发髓系恶性肿瘤，而未经任何放、化学治疗却同时迭患的病例鲜有报道。现将我院收治的一例急性单核细胞白血病迭患多发性骨髓瘤的病例报道如下。

2. 病例资料

患者男性，66 岁，因纳差、乏力伴上腹部疼痛 5 天于 2018-04-20 入临沂市中心医院血液科，查体：贫血貌，齿龈增生，胸骨压痛，浅表淋巴结未及肿大，右侧腹部压痛，肝脾肋下未及。完善血常规：白细胞 1.09 × 10^9/L，血红蛋白 102 g/L，血小板 246 × 10^9/L，中性粒细胞计数 0.48 × 10^9/L，血沉 44 m/h，网织红细胞计数 75 × 10^9/L。生化：总蛋白 89.40 g/L，白蛋白 28.90 g/L，球蛋白 60.50 g/L，尿素 6.7 mmol/L，肌酐 78 umol/L，钙 2.14 mmol/L，矫正血清钙 2.41 mmol/L，乳酸脱氢酶 224 U/L。免疫球蛋白 G 34.4 g/L，免疫球蛋白 A 0.536 g/l，免疫球蛋白 M 0.451 g/L。血清免疫固定电泳：单克隆免疫球蛋白类型 IgG-λ 型。血清游离轻链组合：λ 轻链 1007 mg/dL，κ 轻链 5 mg/dL，λ/κ 201.5。血清 M 蛋白含量 12 g/L。血 β2-微球蛋白 0.88 mg/L。尿本周氏蛋白电泳阳性。肌钙蛋白 8.97 pg/ml，脑利钠肽前体 60.32 pg/ml。骨髓细胞学：增生活跃，原幼单核细胞占 34%；浆细胞 13%，双核、破裙样浆细胞易见。PB：原幼单核细胞占 17%。骨髓病理：骨髓有核细胞增生程度大致正常(60%)；浆细胞小簇状分布；CD38 散在少及小簇(+)，CD138 散在及小簇(+)；CD56 (−)。免疫分型：1) 12.49%细胞(占有核细胞)表达 CD3、CD117、CD38、HLA-DR，部分表达 CD7、CD33、CD13，不表达 CD3、CD5、CD2、CD4、CD8、CD56、CD15、CD10、CD11b、CD16，考虑为恶性髓系幼稚细胞。2) 8.81%细胞(占有核细胞)表达 CD138、CD38、clamdba，不表达 CD19、CD20、CD56、CD117、ckappa，为恶性单克隆浆细胞。髓系白血病常见融合基因筛查、WT1、CEBPA、C-KIT、FLT3/ITD、NPM1 突变均阴性。FISH：IGH 基因重排、RB1 (13q14)、CKS1B (1q21)、p53 (17p13.1)、13q14.3/13q34 均阴性。骨髓染色体：46，XY。头颅、骨盆、脊柱全长骨骼平片未见骨质破坏。腹部 CT：

右侧腹部肠壁增厚，腹腔多发小淋巴结。因经济原因未能行二代基因测序。根据 2021NCCN 指南诊断：1) 急性单核细胞白血病(M5b，中危)；2) 多发性骨髓瘤(IgG-λ，DS 分期 I 期 A 组，ISS 分期 II 期，R-ISS 分期 II 期，LDH 升高，mSMART 标危)。治疗过程：给予小剂量地西他滨 + 阿克拉霉素 + VRd 方案(硼替佐米 + 来那度胺 + 地塞米松)化疗 2 疗程，MM 评估 PR，但 AML 诱导失败，骨髓涂片仍见 12%原幼单核细胞。患者家属拒绝更换强化疗，采用小剂量地西他滨 + CAG + 硼替佐米方案化疗 1 疗程，化疗后出现肺铜绿假单胞菌、曲霉菌感染，患者家属拒绝继续治疗，终因原发病进展并发重症感染于 2019 年 2 月死亡。

3. 讨论

AML 和 MM 同属于血液系统的恶性肿瘤，文献报道的大多为 MM 患者在应接受化疗或自体移植后发生了治疗相关性髓系肿瘤(therapy-related myeloid neoplasms, t-MN) [1] [2] [3] [4] [5]，而在没有放化疗史的患者身上发生 AML 迭患 MM 的病例非常罕见，仅有个案报道。

AML 和 MM 起源于不同的恶性克隆性细胞，分子生物学特征存在较大的差异，但二者同时发生可能存在共同的凋亡信号通路失控和驱动基因突变。研究认为 RAS/MAPK、NF-kB、PI3K-Akt-mTOR、CXCR4/CXCL、DNA 损伤应答/TP53 途径在 AML 和 MM 发生、发展的过程中发挥了重要作用[6] [7] [8] [9]。由于发病率低，目前文献报道尚未发现存在共同的驱动基因，两类疾病的突变高频基因位于 KRAS、NRSAS、TP53、BRAF、BCL-2 [10] [11] [12]，但能否引起 AML 和 MM 同时发生，尚需进一步研究。本例患者如能进行二代基因测序无疑对 AML 迭患 MM 病例提供了研究价值。AML 迭患 MM 临床上罕见，预后差，虽然以蒽环类药物为基础的 AML 方案、异基因造血干细胞移植和分子靶向抑制剂(硼替佐米、来那度胺、达雷妥尤单抗等)在少数患者中取得了一定的疗效，但大多数患者仍无法治愈[13] [14] [15] [16] [17]。本例患者根据指南诊断 AML (中危)迭患 MM (标危)，AML 侵袭性更高，治疗上应以 AML 为主、MM 为辅的方案，患者及家属拒绝强化疗，选用治疗兼顾的方案进行诱导治疗，但 AML 诱导失败，且出现感染并发症导致继续治疗中断。王鲁群[17]报道了 1 例应用硼替佐米联合 CAG 方案(阿糖胞苷 + 阿克拉霉素 + 粒细胞集落刺激因子)治疗 AML 迭患 MM，缓解期超过 6 个月，更适用于年龄大不适合强化疗的患者。Daniel Kim [15]报道了 1 例 AML 迭患 MM 患者采用治疗兼顾化疗方案，多次诱导失败后接受白消安和环磷酰胺为预处理方案的清髓性异基因造血干细胞移植(allo-SCT)，患者在 SCT 后 421 天无病生存。对于 AML 迭患 MM 患者，SCT 可以作为缓解后的一线治疗选择。Celine Berthon [18]报道 1 例 AML 迭患 MM 患者，治疗上采用“3 + 7”方案诱导缓解，AML 达 CR，但出现严重感染导致无法进行强化巩固治疗，换用阿扎胞苷 + 来那度胺维持治疗，MM 取得 VGPR 疗效(AML 仍 CR)，但此后 MM、AML 相继复发，分别给予阿扎胞苷 + 达雷妥尤单抗(Dara)方案、小剂量阿糖胞苷 + 维奈克拉方案治疗，患者最终死于白血病进展，生存期 5 年。化疗联合新的靶向药物可能延长患者生存期。目前研究最多的是 BCL-2 家族蛋白，其中抗凋亡蛋白 Bcl-2-A1、Bcl-xL、Mcl-1 基因的异常表达与肿瘤细胞对放化疗的敏感性和疾病复发、耐药等关系密切[10] [19] [20]。维奈克拉(Venetoclax)是高选择性 BCL-2 抑制剂，目前已被 FDA 批准用于老年不适合强化疗的急性髓系白血病患者，研究显示 BCL2-A1 低表达、PML-RARA、WT1、FLT3 和 IDH1 突变对 Venetoclax 具有更高的敏感性；相反，TET2、KRAS、PTPN11 和 SF3B1 突变与 Venetoclax 耐药性有关[21] [22]。在多发性骨髓瘤患者中 Venetoclax 适用于存在 t(11; 14)、CyclinD1、BCL-2 高表达、Mcl-1/Bcl-XL 低表达的患者[23]，联合硼替佐米、地塞米松可以克服 Venetoclax 单药治疗的不足，并且表现出和 Dara、卡非佐米相似的疗效[24] [25]。另外，17-在和 MM 中被认为与药物耐药性有关，但体内外试验均证实 17p-并不影响 Venetoclax 在和中的应用[24] [26]。AZD5991 [27]是目前正在临床研究的 MCL-1 抑制剂，可直接与 MCL-1 结合，通过激活依赖型线粒体凋亡途径，诱导癌细胞快速

凋亡，其中作用最显著的是多发性骨髓瘤和急性髓系白血病。AZD5991 和 Venetoclax 的联合应用可以导致 caspase 3 的快速激活，并锐减 MCL-1 的水平，可以有效地克服他们在单药治疗上的耐药性[27]。

4. 总结

综上，AML 迭患 MM 临床罕见，总体生存期短，预后差，目前发病机制不明确，无标准治疗方案，临床上仍需要通过综合评估疾病的分期和危险度分层，免疫球蛋白类型、靶器官损害情况、患者的体能状态和感染情况，有无高危耐药基因及有无分子靶向治疗，尽可能应用多药化疗联合靶向药物、缓解后尽快行异基因造血干细胞移植或在非强化疗的基础上增加新的靶向抑制剂治疗可能提高治疗疗效，减少并发症，改善预后，延长生存期。

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