

• 综 述 •

伴高危细胞遗传学异常的复发难治性多发性骨髓瘤的免疫治疗进展

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[摘 要] 多发性骨髓瘤(multiple myeloma, MM)是一种临床表现和生物学行为具有高度异质性的血液系统恶性肿瘤, 患者的预后与是否存在高危细胞遗传学异常(high risk cytogenetic abnormality, HRCA)密切相关。近年来, 蛋白酶体抑制剂和免疫调节药物在MM中的广泛应用显著改善了患者的生存, 但伴HRCA的高危患者仍面临着药物难治、早期疾病进展和不良预后的挑战, 其治疗策略的探索与优化始终是临床难题。在复发难治的疾病状态下, 后续治疗的选择对高危患者来说至关重要。随着MM治疗进入免疫治疗时代, 新药的不断涌现为患者带来了治疗希望。文章聚焦于伴HRCA的复发难治性MM患者, 综述了单克隆抗体、抗体药物偶联物、双特异性抗体以及嵌合抗原受体T细胞疗法在该类患者中的治疗效果, 旨在探讨最优治疗策略并为临床决策提供指导。

[关键词] 复发难治性多发性骨髓瘤; 高危细胞遗传学异常; 免疫治疗

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Immunotherapy advances in relapsed or refractory multiple myeloma with high-risk cytogenetic abnormalities

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[Abstract] Multiple myeloma(MM) is a hematologic malignancy characterized by high heterogeneity in both its clinical presentation and biological behavior. The prognosis for patients with MM is closely associated with the presence or absence of high-risk cytogenetic abnormality(HRCA). In recent years, although the widespread application of proteasome inhibitors and immunomodulatory drugs in MM has significantly improved survival, high-risk patients with HRCA continue to face challenges such as drug resistance, early disease progression, and poor prognosis. The exploration and optimization of treatment strategies for these patients remain a clinical challenge. In the relapsed or refractory disease state, the choice of subsequent treatment is crucial for high-risk patients. With the advent of the immunotherapy era in MM treatment, the continuous emergence of new drugs has brought hope to patients. This article focuses on patients with relapsed or refractory MM accompanied by HRCA, reviewing the efficacy of monoclonal antibodies, antibody-drug conjugates, bispecific antibodies, and chimeric antigen receptor T cells in these patients, aiming to explore optimal treatment strategies and provide guidance for clinical decision-making.

[Key words] relapsed or refractory multiple myeloma; high-risk cytogenetic abnormality; immunotherapy

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多发性骨髓瘤(multiple myeloma, MM)是以克隆性浆细胞在骨髓中异常增殖为特征的血液系统恶性肿瘤, 目前仍无法治愈^[1]。近年来, 以硼替佐米、伊沙佐米和卡非佐米为代表的蛋白酶体抑制剂

(proteasome inhibitor, PI), 以来那度胺和泊马度胺为代表的免疫调节药物(immunomodulatory drug, IMiD)以及自体造血干细胞移植(autologous hematopoietic stem cell transplantation, auto-HSCT)等治疗改善了MM患者的生存,然而,仍有部分高危疾病特征的患者预后不良^[2-3]。多种因素被视为高危疾病特征,例如临床特征(老年患者、衰弱)、实验室和影像学特征(高肿瘤负荷、肾功能不全、循环浆细胞和髓外浸润)、高危细胞遗传学异常(high risk cytogenetic abnormality, HRCA)以及功能性高危(无其他高危因素,开始治疗后18个月内早期疾病进展),但目前对于高危患者的诊断尚未形成统一标准^[4-5]。

实施精准的风险分层管理是MM诊疗的基石,目前存在多种MM风险分层系统,如国际分期体系(International Staging System, ISS)、修订国际分期体系(Revised International Staging System, R-ISS)、第2次修订的国际分期体系(Second Revision of the International Staging System, R2-ISS)、国际骨髓瘤工作组(International Myeloma Working Group, IMWG)风险分层、梅奥骨髓瘤风险分层(Mayo Stratification of Myeloma and Risk-Adapted Therapy, mSMART)、梅奥附加分期系统(Mayo Additive Staging System, MASS)、

骨髓瘤预后评分系统(Myeloma Prognostic Score System, MPSS)等(表1)^[6-11]。除ISS分期外,细胞遗传学检测已成为各个风险分层系统的核心环节。国际与中国指南均建议在MM初次评估时即进行细胞遗传学分析,采用荧光原位杂交等技术在经过CD138富集分选的浆细胞中捕获异常的细胞遗传学事件^[12-13]。伴HRCA的高危患者常面临治疗耐药和早期疾病复发的问题,在复发难治性MM(re-lapsed or refractory MM, RRMM)患者中,HRCA仍是影响预后的重要因素之一,因此后续治疗方案的选择至关重要^[14]。

过去,存在1个HRCA如del(17p)、TP53突变、t(4;14)、t(14;16)、t(14;20)、1q扩增和del(1p)的患者即为高危,而同时存在2项或3项HRCA的患者分别被定义为双打击和三打击高危患者,以反映更差的生物学特性与临床结局^[15]。随着MM治疗进入三联/四联疗法为主导的新时代,以及auto-HSCT的广泛应用显著改善了患者的生存,基于既往传统疗法建立的预后分层体系已无法准确识别出真正的高危患者。鉴于此,IMWG提出了新的HRCA诊断标准,旨在更精准地预测当前标准治疗下的预后:①del(17p)(克隆比例≥20%)和/或TP53突变;②t(4;14)、

表1 MM常见疾病分期和危险度分层体系
Table 1 Common disease staging and risk stratification systems for MM

ISS	R-ISS	R2-ISS ¹	IMWG	mSMART 4.0	MASS ²	MPSS ³
I: β2-MG<3.5 mg/L; serum albumin≥35 g/L	I: patients with ISS stage I, standard risk cytogenetics, and normal LDH levels.	Low risk: 0 point	High risk: 1. del(17p)(cancer clonal fraction ≥20%) and/or TP53 mutation;	High risk: 1. HRCA: 1.1 del(17p)(cancer clonal fraction ≥20%) and/or TP53 mutation;	I: 0 point	I: 0 point
II: all patients who do not meet the criteria for either stage I or stage III	II: all patients who do not meet the criteria for either stage I or stage III	Low to medium risk: 0.5–1.0 point	2. one of these translocations[t(4;14)or t(14;16)or t(14;20)] co-occurring with gain(1q) and/or del(1p);	1.2 bi-allelic del(1p); 1.3 t(4;14), (14;16), or t(14;20) plus either gain/amp(1q) or del(1p); 1.4 gain/amp(1q) plus del(1p);	II: 1 point	II: 1 point
III: β2-MG≥5.5 mg/L	III: ISS stage III patients who also have HRCA [del(17p), t(4;14)or t(14;16)] or elevated LDH levels	Medium to high risk: 1.5–2.5 points	3. monoallelic del(1p) along with gain(1q), or biallelic del(1p);	2. β2-MG>5.5 mg/L with normal renal function;	III: ≥2 points	III: 2–3 points
–	–	High risk: 3–5 points	4. high β2-MG (≥5.5 mg/L) with normal creatinine (<1.2 mg/dL)	3. high plasma cell S-phase; 4. primary plasma cell leukemia; 5. newly diagnosed myeloma with extramedullary disease	–	IV: 4–7 points

β2-MG: β2-microglobulin; LDH: lactate dehydrogenase. ¹Weighted score: ISS stage II (1 point), ISS stage III (1.5 points), del(17p) (1 point), high LDH (1 point), t(4;14) (1 point), gain/amp(1q) (0.5 point). ²Weighted score: high-risk IgH translocation, gain/amp(1q), chromosome 17 abnormality, ISS stage III, and elevated LDH are each assigned 1 point. ³Weighted score: thrombocytopenia (2 points), elevated LDH (1 point), ISS stage III (2 points), presence of one HRCA among t(4;14), t(14;16), del(17p), or gain/amp(1q) (1 point), presence of two or more such HRCA (2 points).

t(14; 16)或t(14; 20)与1q扩增和/或del(1p)共存;
③单等位基因del(1p)与1q扩增共存或双等位基因del(1p),该标准可识别出约20%的高危患者,在目前标准治疗下仍预后不佳^[8]。

近年来,细胞免疫治疗已成为MM的一种新型治疗模式,新型免疫疗法在多个临床研究中显示出令人鼓舞的治疗效果。然而,免疫疗法能否克服HRCA导致的不良预后尚不明确。鉴于目前的临床研究通常将存在上述任意1个HRCA视作高危分组的划分依据,文章也沿用此标准定义高危人群,综述了单克隆抗体(monoclonal antibody, mAb)、抗体药物偶联物(antibody-drug conjugate, ADC)、双特异性抗体(bispecific antibody, BsAb)和嵌合抗原受体T细胞(chimeric antigen receptor T-cell, CAR-T)疗法在伴HRCA的RRMM患者中的治疗进展(图1)。

1 mAb

mAb能够特异性识别并结合靶细胞表面的特定抗原,通过抗体依赖性细胞介导的细胞毒性、补体依赖性细胞毒性、抗体依赖性细胞吞噬及直接诱导细胞凋亡等途径杀伤并清除MM细胞。此外,

mAb还可以对骨髓微环境进行调节,进而增强机体的抗肿瘤免疫反应。

1.1 靶向CD38的mAb

达雷妥尤单抗(Daratumumab, Dara)是首个靶向CD38的全人源IgG1-κ mAb,在Ⅱ期GEN501和SIRIUS临床试验中,Dara单药治疗在RRMM患者中显示出良好的疗效^[16-17]。CASTOR研究比较了RRMM患者接受Dara-硼替佐米-地塞米松(Dara-Vd)或硼替佐米-地塞米松(Vd)方案的生存差异,研究定义的HRCA包括t(4; 14)、t(14; 16)或del(17p)。与Vd方案相比,Dara-Vd治疗显著提高了伴HRCA患者的中位无进展生存期(progression free survival, PFS)[6.2个月 vs. 12.6个月,风险比(hazard ratio, HR)=0.41, 95%置信区间(95% confidence interval, 95% CI):0.21~0.83, P=0.010 6]^[18]。高危人群总生存期(overall survival, OS)随访结果示Dara-Vd组的OS达到38.4个月,长于Vd组的28.8个月,但OS获益差异无统计学意义(HR=0.77, 95% CI: 0.41~1.46)^[19]。CANDOR试验中,在卡非佐米联合地塞米松(Kd)方案的基础上加用Dara(Dara-Kd),中位随访28个月后,高危亚组患者的中位PFS为11.2个月,优于Kd

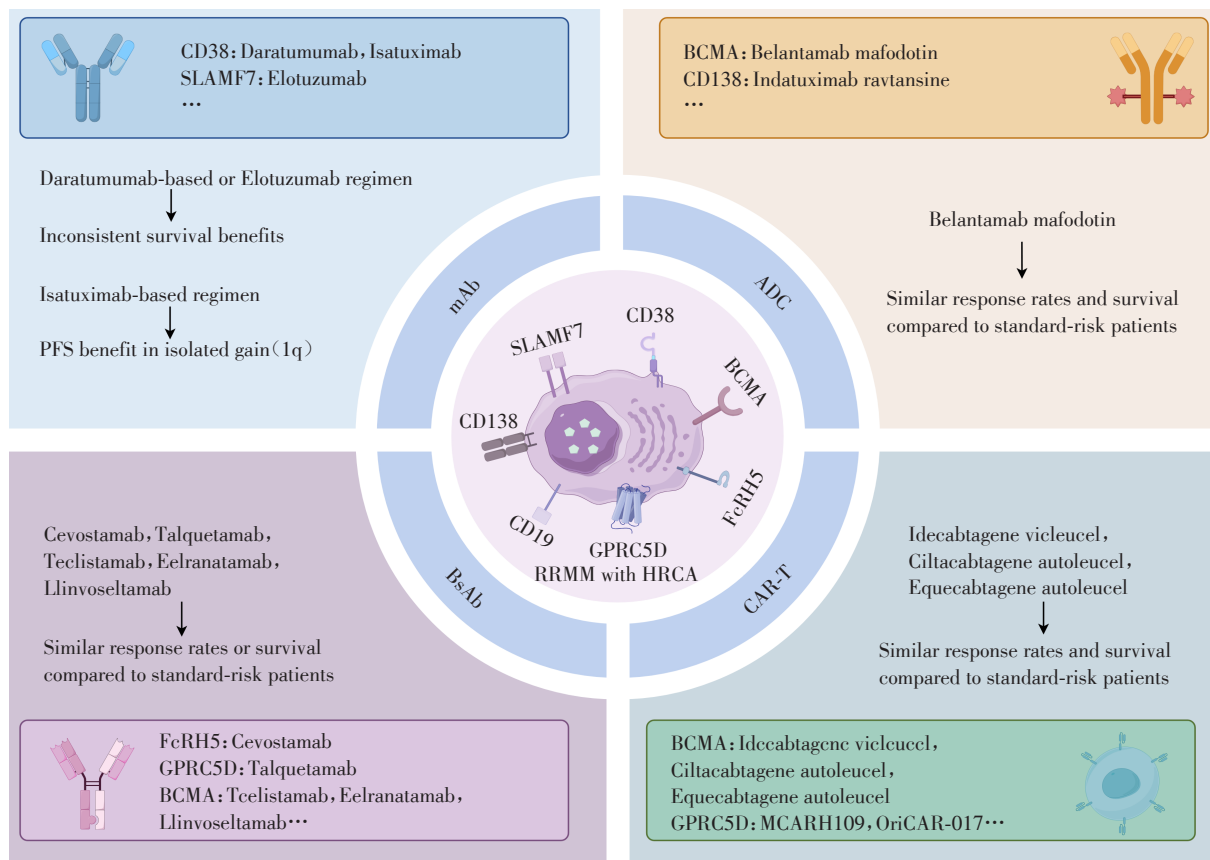


图1 伴HRCA的RRMM患者的免疫治疗

Figure 1 Immunotherapy for RRMM patients with HRCA

组的7.4个月($HR=0.56$, $95\%CI: 0.37\sim0.93$);而在标危亚组中,Dara-Kd方案尚未达到中位PFS。中位随访超过4年后,Dara-Kd延长了高危患者的中位OS(34.3个月 *vs.* 17.1个月, $HR=0.52$, $95\%CI: 0.29\sim0.94$),但与标危患者(中位OS未达到)相比,生存期仍不令人满意^[20-21]。在POLLUX和APOLLO临床试验中,Dara分别与来那度胺及地塞米松(Dara-Rd)和泊马度胺及地塞米松(Dara-Pd)联用,Dara-Rd治疗较Rd治疗显著延长了高危患者的中位PFS[26.8个月 *vs.* 8.3个月($HR=0.34$, $95\%CI: 0.16\sim0.72$, $P=0.0035$)],然而OS获益并不显著[40.0个月 *vs.* 23.6个月($HR=0.70$, $95\%CI: 0.41\sim1.20$)];Dara-Pd治疗在伴HRCA的患者中未显示出有统计学意义的PFS获益[5.8个月 *vs.* 4.0个月($HR=0.85$, $95\%CI: 0.49\sim1.44$)]^[22-26]。因此,在高危RRMM患者中,Dara与PI或IMiD联用时的PFS与OS获益不一。

艾沙妥昔单抗(Isatuximab, Isa)是一种人鼠嵌合的CD38 mAb, ICARIA-MM和IKEMA两项临床研究分别分析了Isa-泊马度胺-地塞米松(Isa-Pd)和Isa-卡非佐米-地塞米松(Isa-Kd)方案在伴HRCA[t(4;14)、t(14;16)、del(17p)或1q扩增]的RRMM患者中的疗效。结果显示,对伴t(4;14)、t(14;16)或del(17p)的患者,Isa联合方案未能带来有统计学意义的PFS和OS获益;而对于伴孤立性1q扩增的患者,Isa联合方案显示出了PFS获益[Isa-Pd *vs.* Pd: 11.2个月 *vs.* 4.6个月($HR=0.50$, $95\%CI: 0.28\sim0.88$);Isa-Kd *vs.* Kd: 未达到 *vs.* 16.2个月($HR=0.46$, $95\%CI: 0.22\sim0.97$)],但该类人群的OS获益仍不显著^[27-32]。因此,对于伴孤立性1q扩增的RRMM患者,Isa联合方案展现出了明确的PFS优势。

对伴HRCA的高危患者,两种靶向CD38的mAb均呈现出了一定的生存获益趋势,Isa在伴孤立性1q扩增的患者中更具优势。在安全性方面,两者报告的 ≥ 3 级血液学不良事件(adverse event, AE)和感染发生率相近。

1.2 靶向信号淋巴细胞激活分子F7(signaling lymphocytic activation molecule family 7, SLAMF7, 又称CS1)的mAb

埃罗妥珠单抗(Elotuzumab, Elo)是一种靶向SLAMF7的免疫刺激性mAb。ELOQUENT-2研究结果显示在来那度胺-地塞米松方案中加入Elo(Elo-Rd)延长了伴del(17p)、1q扩增和t(4;14)的RRMM患者的中位PFS, HR值分别为0.65($95\%CI: 0.45\sim0.94$)、0.75($95\%CI: 0.56\sim0.99$)和0.53($95\%CI:$

$0.29\sim0.95$),并且在伴del(17p)的患者中观察到了持续的OS获益(中位OS: 50.1个月 *vs.* 36.4个月, $HR=0.71$, $95\%CI: 0.46\sim1.00$),在该研究中Elo可能改善了del(17p)带来的不良预后^[33-34]。但在ELOQUENT-3试验纳入的来那度胺难治的高危RRMM患者中,Elo-泊马度胺-地塞米松(Elo-Pd)方案并未表现出有统计学意义的PFS[Elo-Pd *vs.* Pd: 6.5个月 *vs.* 2.5个月($HR=0.52$, $95\%CI: 0.22\sim1.25$)]和OS(详细OS结果未报告; $HR=0.83$, $95\%CI: 0.38\sim1.83$)获益^[35-36]。因此,Elo的疗效可能受细胞遗传学背景及治疗线数的影响,需要更多的临床结果加以验证。

综上,基于mAb的治疗方案在高危RRMM患者中可能存在部分生存获益,各临床试验具体生存结果见表2。

2 ADC

ADC是一类通过连接器将细胞毒性药物与mAb连接形成的药物,与靶细胞结合后,小分子细胞毒性药物被MM细胞内吞,进而诱导细胞死亡。

玛贝兰妥单抗(Belantamab mafodotin)是一种靶向B细胞成熟抗原(B cell maturation antigen, BCMA)的ADC。在II期DREAMM-2临床试验中,既往接受 ≥ 3 线治疗的RRMM患者接受了玛贝兰妥单抗单药治疗,中位随访13个月后,中位PFS和OS分别达到了2.8个月和13.7个月。值得注意的是,在伴del(17p)、t(4;14)、t(14;16)或1q扩增的高危患者中,总缓解率(overall response rate, ORR)达到29%,与总体人群ORR(32%)相当^[37]。此外,在一项真实世界研究中,接受玛贝兰妥单抗单药治疗的高危和标危患者的中位OS均为9.2个月,与总体人群相似^[38]。DREAMM-7研究比较了玛贝兰妥单抗、硼替佐米和地塞米松(B-Vd)与Dara-Vd在494例RRMM中的疗效,两组高危患者的比例接近(B-Vd: 28% *vs.* Dara-Vd: 27%)。中位随访28.2个月后,B-Vd组和Dara-Vd组的中位PFS分别为36.6个月和13.4个月($HR=0.41$, $95\%CI: 0.31\sim0.53$, $P<0.001$),在标危亚组中也观察到了B-Vd方案的PFS获益($HR=0.36$, $95\%CI: 0.22\sim0.58$)^[39]。更长时间(39.4个月)的OS随访结果表明,B-Vd方案较Dara-Vd方案降低了高危患者50%($95\%CI: 0.28\sim0.87$)的死亡风险,B-Vd组高危患者的3年OS率为75%,高于Dara-Vd组(57%),且与标危患者接近(74%)^[40]。上述各项研究结果均证实玛贝兰妥单抗能够为高危患者带来生存获益,并且其疗效明显优于基于mAb的治疗方案,为患者提

表2 mAb在伴HRCA的RRMM患者中的临床试验列表
Table 2 List of clinical trials involving mAb in RRMM patients with HRCA

Clinical trial	Regimen and sample size	HRCA	Median PFS analysis in high risk patients(months)	Median OS analysis in high risk patients(months)	Prior lines of therapy
CASTOR	Dara-Vd(<i>n</i> =30) <i>vs.</i> Vd(<i>n</i> =27)	t(4; 14), t(14; 16), del(17p)	12.6(Dara-Vd) <i>vs.</i> 6.2(Vd); HR=0.41(0.21–0.83), <i>P</i> =0.010 6	38.4(Dara-Vd) <i>vs.</i> 28.8(Vd); HR=0.77(0.41–1.46)	Median 2 (1–10)
CANDOR	Dara-Kd(<i>n</i> =45) <i>vs.</i> Kd(<i>n</i> =26)	t(4; 14), t(14; 16), del(17p)	11.2(Dara-Kd) <i>vs.</i> 7.4(Kd); HR=0.56(0.37–0.93)	34.3(Dara-Kd) <i>vs.</i> 17.1(Kd); HR=0.52(0.29–0.94)	1–3
POLLUX	Dara-Rd(<i>n</i> =35) <i>vs.</i> Rd(<i>n</i> =35)	t(4; 14), t(14; 16), del(17p)	26.8(Dara-Rd) <i>vs.</i> 8.3(Rd); HR= 0.34(0.16–0.72)	40.0(Dara-Rd) <i>vs.</i> 23.6(Vd); HR=0.70(0.41–1.20)	≥1
APOLLO	Dara-Pd(<i>n</i> =39) <i>vs.</i> Pd(<i>n</i> =35)	t(4; 14), t(14; 16), del(17p)	5.8(Dara-Pd) <i>vs.</i> 4.0(Pd); HR=0.85(0.49–1.44)	Not reported	≥1
ICARIA-MM	Isa-Pd(<i>n</i> =24) <i>vs.</i> Pd(<i>n</i> =36)	t(4; 14), t(14; 16), del(17p)	7.5(Isa-Pd) <i>vs.</i> 3.7(Pd); HR=0.66(0.33–1.28)	15.4(Isa-Pd) <i>vs.</i> 15.6(Pd); HR=0.87(0.47–1.62)	≥2
	Isa-Pd(<i>n</i> =56) <i>vs.</i> Pd(<i>n</i> =29)	Isolated gain (1q)	11.2 (Isa - Pd) <i>vs.</i> 4.6 (Pd) ; HR= 0.50(0.28–0.88)	21.3(Isa-Pd) <i>vs.</i> 13.9(Pd); HR=0.72(0.48–1.07)	
IKEMA	Isa-Kd(<i>n</i> =42) <i>vs.</i> Kd(<i>n</i> =31)	t(4; 14), t(14; 16), del(17p)	Not reached(Isa-Kd) <i>vs.</i> 18.20(Kd); HR=0.72(0.36–1.45)	Not reported	Median 2 (1–3)
	Isa-Kd(<i>n</i> =75) <i>vs.</i> Kd(<i>n</i> =52)	Isolated gain(1q)	Not reached(Isa-Kd) <i>vs.</i> 16.20(Kd); HR=0.46(0.22–0.97);	Not reported	
ELOQUENT-2	Elo - Rd <i>vs.</i> Rd (<i>n</i> =unknown)	t(4; 14), gain (1q), del(17p)	Not reported; HR: del(17p): 0.65 (0.45–0.94); gain(1q): 0.75(0.56– 0.99); t(4; 14): 0.53(0.29–0.95)	del(17p): 50.1(Elo-Rd) <i>vs.</i> 36.4 (Rd); HR=0.71(0.46–1.00)	1–3
ELOQUENT-3	Elo-Pd(<i>n</i> =16) <i>vs.</i> Pd(<i>n</i> =18)	t(4; 14), t(14; 16), gain(1q), del(17p)	6.5(Elo-Pd) <i>vs.</i> 2.5(Pd); HR=0.52(0.22–1.25)	Not reported; HR=0.83(0.38–1.83)	≥2

供了一个更佳的治疗选择。

一项开放标签 I / II a 期研究评估了靶向 CD138 的 ADC 药物 Indatuximab ravtansine 联合地塞米松与来那度胺或泊马度胺的方案在 RRMM 患者中的疗效。在 57 例可获得基线细胞遗传学数据的患者中, 9 例为高危患者, 分别有 4、2 和 1 例患者达到了部分缓解(partial response, PR)、非常好的部分缓解(very good partial response, VGPR)和完全缓解(complete response, CR)^[41]。该药物在高危患者中的疗效已获得初步验证, 其确切的临床获益有待通过扩大样本量和延长随访期后的研究数据来进一步确认。

3 T 细胞重定向疗法(T-cell redirection therapy, TCR)

3.1 BsAb

BsAb 能够同时结合 MM 细胞表面的特异性抗原和 T 细胞表面的 CD3 受体, 形成免疫突触, 从而激活免疫反应并杀伤肿瘤细胞。

3.1.1 靶向 BCMA 的 BsAb

特立妥单抗(Teclistamab)是首个获批用于治疗 RRMM 的靶向 BCMA×CD3 的 T 细胞重定向双特异性 IgG4 抗体。在 MajesTEC-1 研究中, 共有 165 例 RRMM 患者接受了特立妥单抗单药治疗, 既往中位治疗线数为 5, 中位随访 14.1 个月后, ORR 达到了 63.0%, 分别有 58.8% 和 39.4% 的患者达到了 VGPR 和 CR。在 148 例可获得细胞遗传学数据的患者中, 38 例(25.7%)患者存在至少 1 个 HRCA[t(4; 14)、t(14; 16)或 del(17p)]。在高危亚组分析中, 特立妥单抗的有效率与总体人群一致^[42]。此外, 该试验的 C 队列结果显示, 曾接受靶向 BCMA 的 ADC 或 CAR-T 治疗患者的 ORR 为 52.5%, 其中 12 例(33%)高危患者的 ORR 为 33%^[43]。MajesTEC-3 研究评估了特立妥单抗联合 Dara 对比 Dara-Vd 或 Dara-Pd 方案在既往接受 1~3 线治疗 RRMM 患者中的疗效。中位随访 34.5 个月时, 特立妥单抗联合 Dara 组的中位 PFS 显著长于 Dara-Vd 或 Dara-Pd 组(*P* < 0.001); 估算的

3年PFS率分别为83.4%和29.7%(HR=0.17,95%CI:0.12~0.23)。亚组分析显示,在高危和标危患者中,HR分别为0.15(95%CI:0.09~0.25)和0.16(95%CI:0.09~0.27),提示该联合治疗方案在不同细胞遗传学风险的患者中具有一致的生存获益^[44]。

埃纳妥单抗(Elranatamab)是一种靶向BCMA及CD3的人源化特异性IgG2抗体。MagnetisMM-1临床研究报告称,既往中位5线治疗的55例RRMM患者接受皮下埃纳妥单抗单药治疗后,ORR、CR率(CR rate,CRR)、中位PFS、中位OS分别为63.6%、38.2%、11.8个月和21.2个月。在16例(29.1%)携带t(4;14)、t(14;16)或del(17p)的患者中,ORR达到50%,其中有7例(43.8%)和4例(25.0%)患者达到了VGPR和CR^[45]。此外,在MagnetisMM-3研究中观察到高危患者的ORR与总体人群相近^[46]。目前多项基于埃纳妥单抗治疗RRMM的临床试验仍在进行中,包括埃纳妥单抗联合Kd或Maplirpaccept用于治疗RRMM患者(MagnetisMM-20),以及埃纳妥单抗单药、埃纳妥单抗联合Dara对比Dara-Pd用于治疗RRMM患者(MagnetisMM-5)。

LINKER-MM1试验报告了全人源化靶向BCMA及CD3的BsAb产品Linoseltamab(REGN5458)在RRMM中的疗效,该试验共入组282例患者,其中117例患者接受了全剂量(200 mg)的Linoseltamab治疗,既往中位治疗线数为5。中位随访14.3个月后,全剂量组的ORR为70.9%,分别有74例(63.2%)和58例(49.6%)患者达到了VGPR和CR。在46例(39.3%)存在t(4;14)、t(14;16)或del(17p)的患者中,有31例(67.4%)实现了疾病缓解,与标危患者的缓解率相近(73.2%)^[47]。

上述3款靶向BCMA的BsAb在多线治疗后的高危患者中的初步疗效可观。在安全性方面,最常见的≥3级AE均为血液学毒性,包括中性粒细胞减少(41.9%~71.0%)、贫血(30.8%~50.9%)和血小板减少(21.2%~29.1%),其中埃纳妥单抗发生率最高,特立妥单抗次之,Linoseltamab最低;而≥3级细胞因子释放综合征(cytokine release syndrome, CRS)的发生率均很低(0~0.9%)。

3.1.2 非靶向BCMA的BsAb

塔奎妥单抗(Talquetamab)是首个获批用于治疗RRMM的靶向G蛋白偶联受体C类5组成员D(G protein-coupled receptor class C group 5 member D, GPRC5D)及CD3的BsAb。MonumenTAL-1临床研究入组了375例RRMM患者,其中143例和154例未

接受过TCR疗法的患者分别接受每周1次0.4 mg/kg和每2周1次0.8 mg/kg的塔奎妥单抗单药治疗,既往TCR治疗组的78例患者接受上述两种剂量方案之一的治疗,各组的既往中位治疗线数分别为5、4.5和6。在中位随访25.6个月、19.4个月和16.8个月后,3组患者的ORR分别达到74%、69%和67%,中位PFS分别为7.5个月、11.2个月和7.7个月。伴t(4;14)、t(14;16)或del(17p)的高危患者分别占各组的31%、30%和37%。亚组分析结果显示每周1次0.4 mg/kg剂量组的高危患者中位PFS为6.7个月,标危患者为8.5个月;值得注意的是,在每2周1次0.8 mg/kg剂量组中,高危患者中位PFS达到了18.0个月,长于标危组的10.3个月,但差异无统计学意义^[48]。在一项多中心的真实世界研究中,塔奎妥单抗单药在既往接受中位6线治疗且可评估疗效的98例RRMM患者中的ORR达到了73%。其中70%的患者至少存在t(4;14)、t(14;16)、t(14;20)、del(17p)或1q扩增定义的1种HRCA,高危患者的ORR为76%,标危患者的ORR为70%,两组差异无统计学意义($P=0.56$)^[49]。因此,塔奎妥单抗单药治疗能为伴HRCA的RRMM患者带来治疗获益。在安全性方面,因为GPRC5D在角化上皮结构组织中表达,所以皮肤、指甲、口腔黏膜的AE较为常见。

Cevostamab(BFCR4350A)是一种靶向Fc受体同源物5(Fc receptor homolog 5, FcRH5)和CD3的BsAb。I期临床试验GO39775纳入了51例既往中位6线治疗的RRMM患者,包括曾接受ADC、BsAb或CAR-T治疗(含靶向BCMA)的患者。在Cevostamab单药治疗组,观察到29例患者中有15例(51.7%)出现疾病缓解,伴1q扩增、t(4;14)、t(14;16)或del(17p)的17例高危患者中9例(52.9%)出现疾病缓解^[50]。Cevostamab有望克服HRCA对预后的不良影响,但长期生存的获益需要延长随访时间。

3.1.3 BsAb联合用药

RedirecTT-1临床试验探究了特立妥单抗和塔奎妥单抗联合用药治疗RRMM的疗效,44例接受推荐II期剂量方案的患者ORR达78%,伴HRCA的8例高危患者中6例(75%)疾病缓解^[51]。

综上,多项临床研究均表明了BsAb在经历多线复发且伴HRCA患者中的初步疗效,但仍需要增加样本量并延长随访时间以证实生存获益。

3.2 CAR-T疗法

CAR-T疗法通过采集患者的外周血T细胞,经

基因修饰技术将带有特异性抗原识别结构域的CAR基因转入T细胞并回输给患者。回输的CAR-T细胞与MM细胞表面特异性抗原结合并激活T细胞内的信号通路,发挥靶向杀伤肿瘤细胞的作用。

3.2.1 靶向BCMA的CAR-T疗法

KarMMa研究报道了靶向BCMA的艾基维仑赛(Idecabtagene vicleucel)在既往接受 ≥ 3 线系统性治疗的RRMM患者中的疗效。经过环磷酰胺和氟达拉滨的淋巴细胞清除预处理,128例患者接受目标剂量的艾基维仑赛输注。研究报道所有患者的ORR、CRR、中位缓解持续时间(duration of response, DOR)、中位PFS分别为73%、33%、10.7个月和8.8个月,其中45例患者存在由del(17p)、t(4;14)或t(14;16)定义的HRCA,高危亚组的ORR、CRR、中位DOR、中位PFS分别为69%、31%、10.7个月和8.8个月,标危患者的ORR、CRR、中位DOR、中位PFS分别为80%、38%、10.9个月和10.4个月,这表明艾基维仑赛在高危人群中实现了与标危患者相似的疾病缓解率和生存期^[52]。KarMMa-3研究比较了艾基维仑赛与标准方案[包括Dara-Pd、Dara-Vd、IRd(伊沙佐米、来那度胺和地塞米松)、Kd和Elo-Pd]在既往接受2~4线治疗的RRMM中的疗效。中位随访18.6个月后,艾基维仑赛治疗组和标准方案组的中位PFS分别为13.3个月和4.4个月(HR=0.49, 95%CI: 0.38~0.65, $P < 0.001$)。两组中高危患者比例接近(42% vs. 46%),亚组分析结果显示中位PFS分别为11.9个月和4.2个月(HR=0.61, 95%CI: 0.41~0.90),而两组标危患者的中位PFS分别为14.7个月和4.8个月(HR=0.44, 95%CI: 0.31~0.63)^[53]。此外,一项II期KarMMa-2(NCT03601078)研究正在进行中,该试验旨在评估艾基维仑赛在RRMM患者和高危MM患者中的疗效和安全性。

西达基奥仑赛(Ciltacabtagene autoleucel)是具有两个靶向BCMA单域抗体的CAR-T疗法,LEGEND-2试验纳入74例既往接受中位3线治疗的RRMM患者在淋巴细胞清除后接受西达基奥仑赛治疗。在42例可获得细胞遗传学数据的患者中,15例(35.7%)存在del(17p)、t(4;14)或t(14;16),结果显示高危患者与标危患者的CRR相近(80% vs. 66.7%)且差异无统计学意义。此外,两组的中位DOR、中位OS与中位PFS差异也无统计学意义(P 值分别为0.212、0.737和0.684)。因此,西达基奥仑赛有望使高危RRMM患者达到与标危患者相当的缓解水平和生存获益^[54]。III期CARTITUDE-4研究比较了来那度

胺难治的患者接受西达基奥仑赛输注与标准方案[包括PVd(泊马度胺、硼替佐米和地塞米松)和Dara-Pd]的生存结局。中位随访33.6个月后,西达基奥仑赛组的中位PFS尚未达到,而标准治疗组为11.8个月(HR=0.29, 95%CI: 0.22~0.39),两组的中位OS均未达到(HR=0.55, 95%CI: 0.39~0.79, $P=0.009$)。携带t(4;14)、t(14;16)、del(17p)或1q扩增的高危患者约60%,双打击患者约20%。结果表明,西达基奥仑赛为标危患者带来显著的PFS获益(HR=0.32, 95%CI: 0.18~0.59),OS也呈现改善趋势(HR=0.62, 95%CI: 0.33~1.19)。与此同时,该疗法显著改善了高危患者的PFS(HR=0.29, 95%CI: 0.20~0.41)和OS(HR=0.54, 95%CI: 0.35~0.85)。在双打击患者中PFS获益同样显著(HR=0.30, 95%CI: 0.17~0.54),OS也呈改善趋势(HR=0.57, 95%CI: 0.30~1.07)^[55]。

伊基奥仑赛(Equecabtagene autoleucel)是一种全人源化的靶向BCMA的CAR-T产品,在一项I期研究中,18例既往中位4线治疗的RRMM患者接受了CT103A治疗,其中13例(72.2%)患者存在del(17p)、t(4;14)、t(14;16)、t(14;20)或1q扩增。中位随访45.0个月后,高危组和标危组的ORR分别为85%和60%($P=0.623$),生存分析结果提示两组的PFS和OS差异均无统计学意义(P 值分别为0.2169和0.3703),值得注意的是,双打击患者(6例,33%)和非双打击患者的PFS和OS差异也无统计学意义(P 值分别为0.3500和0.4909)。因此,伊基奥仑赛在高危RRMM患者中展现了具有前景的疗效^[56]。

综上,多项研究证实,对于伴HRCA且经历多线治疗复发的患者,靶向BCMA的CAR-T疗法已经显示可观的疗效,其疾病缓解率及生存结局与标危患者相近。与包括mAb的标准疗法相比,CAR-T疗法的疾病进展或死亡风险更低,并有望克服HRCA导致的不良预后。在安全性方面,艾基维仑赛和西达基奥仑赛的常见 ≥ 3 级AE为血液学毒性,包括中性粒细胞减少(76%~90%)、贫血(36%~60%)、血小板减少(42%~52%),接受西达基奥仑赛治疗的患者中 ≥ 3 级CRS发生率高于艾基维仑赛(9.5% vs. 5.0%),而伊基奥仑赛的 ≥ 3 级AE发生率均明显低于上述两种产品。表3总结了ADC及TCR治疗高危RRMM患者的部分临床试验结果。

3.2.2 靶向GPC5D的CAR-T疗法

一项I期临床试验报告了在既往中位6线治疗的17例(13例伴HRCA)患者中,靶向GPC5D的

CAR-T疗法MCAH109的ORR为71%, 分别有10例(59%)和6例(35%)患者达到了VGPR和CR^[57]。POLARIS研究报道了另一款靶向GPC5D的CAR-T产品 OriCAR-017 的疗效, 10例(6例伴HRCA)RRMM患者的ORR为100%, 6例达到了CR, 4例达到VGPR^[58]。靶向GPC5D的CAR-T疗法已初步展

现良好疗效, 期待高危亚组分析的结果。
3.2.3 双靶点CAR-T疗法
靶向BCMA的CAR-T治疗在RRMM中展示出显著的临床疗效, 但BCMA抗原逃逸常导致疾病复发, 在BCMA CAR-T产品中同时靶向另一个抗原以减轻BCMA逃逸介导的疾病复发, 即双靶点CAR-T

表3 ADC和TCR在伴HRCA的RRMM患者中的临床试验列表
Table 3 List of clinical trials involving ADC and TCR in RRMM patients with HRCA

Clinical trial	Regimen and sample size	HRCA	ORR/CRR (%)	Survival outcome	Prior lines of therapy
DREMM-2	Belantamab mafodotin(<i>n</i> =41)	t(4; 14), t(14; 16), del(17p), gain(1q)	ORR: 29	Not reported	≥3
DERMM-7	Belantamab mafodotin-Vd(<i>n</i> =67) <i>vs.</i> Dara-Vd(<i>n</i> =69)	t(4; 14), t(14; 16), del(17p)	Not reported	HR (median PFS)=0.36(0.22–0.58); HR (median OS)=0.50(0.28–0.87); 3-year OS rate: 75% <i>vs.</i> 57%	≥1
MajesTEC-1	Teclistamab(<i>n</i> =38)	t(4; 14), t(14; 16), del(17p)	ORR: 60.5	Not reported	Median 5 (2–14)
MajesTEC-3	Teclistamab plus Dara (<i>n</i> =20) <i>vs.</i> Dara - Vd/ Dara-Pd(<i>n</i> =78)	t(4; 14), t(14; 16), del(17p)	Not reported	HR (prespecified 3-year PFS rate)= 0.15(0.09–0.25)	1–3
MagnetisMM-1	Elranatamab(<i>n</i> =16)	t(4; 14), t(14; 16), del(17p)	ORR: 50	Not reported	Median 5
LINKER-MM1	Linvoseltamab(<i>n</i> =46)	t(4; 14), t(14; 16), del(17p)	ORR: 67.4	Not reported	Median 5 (2–16)
MonumenTAL-1	Talquetamab(<i>n</i> =106)	t(4; 14), t(14; 16), del(17p)	Not reported	Median PFS: 6.7 months(0.4 mg/kg), 18.0 months(0.8 mg/kg)	4–8
GO39775	Cevostamab(<i>n</i> =17)	t(4; 14), t(14; 16), del(17p), gain(1q)	ORR: 52.9	Not reported	Median 6 (2–15)
RedirecTT-1	Teclistamab plus Talquetamab(<i>n</i> =8)	t(4; 14), t(14; 16), del(17p)	ORR: 75	Not reported	Median 4 (2–10)
KarMma	Idecabtagene vicleucel(<i>n</i> =45)	t(4; 14), t(14; 16), del(17p)	ORR: 69; CRR: 31	Median DOR: 10.7 months; median PFS: 8.8 months	≥3
KarMma-3	Idecabtagene vicleucel (<i>n</i> =107) <i>vs.</i> standard regimens(<i>n</i> =61)	t(4; 14), t(14; 16), del(17p)	Not reported	Median PFS: 11.9 months <i>vs.</i> 4.2 months; HR=0.61(0.41–0.90)	2–4
LEGEND-2	Ciltacabtagene auto-leucel(<i>n</i> =15)	t(4; 14), t(14; 16), del(17p)	CRR: 80	<i>P</i> value between high risk and standard risk groups: 0.212 (median DOR), 0.737 (median OS), 0.684 (median PFS)	Median 3 (1–9)
CARTITUDE-4	Ciltacabtagene auto-leucel(<i>n</i> =123) <i>vs.</i> standard regimens (<i>n</i> =132)	t(4; 14), t(14; 16), del(17p), gain(1q)	Not reported	HR (median PFS)=0.29(0.20–0.41); HR (median OS)=0.54(0.35–0.85)	1–3
ChiCTR 1800018137	Equecabtagene auto-leucel(<i>n</i> =13)	t(4; 14), t(14; 16), t(14; 20), del(17p), gain(1q)	ORR: 80	<i>P</i> value between high risk and standard risk groups: 0.216 9 (median PFS), 0.370 3 (median OS)	Median 4 (3–6)

疗法^[59]。GC012F是一种同时靶向BCMA和CD19的双靶点CAR-T疗法,在一项I期开放标签研究中,29例既往中位5线治疗的患者在淋巴细胞清除后接受GC012F输注,其中26例为高危患者,随访截止时,ORR、CRR和VGPR率分别达到了93.1%、82.8%和89.7%^[60]。50例(34例伴HRCA)RRMM患者接受了另一款靶向BCMA和CD19的BC19 CAR-T治疗,研究结果示,中位随访11个月后,ORR、中位PFS、中位OS和中位DOR分别为92%、19.7个月(95%CI: 5.0~34.4个月)、19.7个月(95%CI: 7.7~31.7个月)和未达到,高危亚组的ORR也达到了91%^[61]。一项I期临床试验报告了靶向BCMA和CD38的人源化双特异性BM38 CAR-T在23例(17例伴HRCA)RRMM患者中的治疗结果,中位随访9个月时,20例(87%)患者达到CR和微小残留病灶阴性,其中12例(52%)达到严格意义CR^[62]。此外,一项评估靶向BCMA和CS1的双特异性CAR-T产品在16例(9例伴HRCA)RRMM患者中的ORR为81%,并有6例患者达到严格意义CR^[63]。目前的研究结果显示双靶点CAR-T治疗在RRMM患者中初具疗效,期待这些CAR-T产品有更长远的生存获益。

3.3 TCR疗法面临的挑战

虽然在新型疗法下伴HRCA的患者缓解率有所提高,但TCR疗法的疗效仍受到一系列因素挑战,可归纳为疾病特征、肿瘤抗原下调和患者免疫状态三大方面。在疾病特征方面,高肿瘤负荷(骨髓浆细胞比例高)和髓外病变是公认最重要的预后不良因素,它们提示肿瘤侵袭性强且难以清除。对3类药物反应差以及既往靶向治疗暴露是预测疗效不佳的关键指标,肿瘤靶抗原的下调与缺失是TCR疗法耐药的核心机制之一,高水平的可溶性BCMA表达也可能干扰TCR功能,且这些患者往往伴有较高的肿瘤负荷或广泛的髓外病变,从而限制其临床疗效^[64-65]。最后,患者的免疫状态(如T细胞耗竭、免疫抑制性肿瘤微环境抑制T细胞的活化与增殖)和较差的体能状态不仅影响CAR-T的扩增和持久性,也增加了治疗相关AE风险^[66-68]。因此,在临床实践中,需对这些高危因素进行全面评估,以指导更积极的预处理和优化治疗策略。

4 总结与展望

综上所述,基于现有已发表的研究结果,RRMM患者在免疫治疗下的预后得到了显著改善。值得注意的是,BsAb、ADC和CAR-T治疗在伴HRCA的经多

线治疗复发的患者中展现出初步的潜力,并显示出改善HRCA相关不良预后的趋势,有望使这部分高危患者获得与标危群体相近的疾病缓解和生存结局。目前,多项针对MM的免疫治疗临床试验仍在积极开展,期待未来更大样本量、更长随访时间的研究进一步验证上述结论。随着免疫治疗的发展,现有的疾病风险分层体系将面临调整与更新,未来临床研究也需统一HRCA的诊断标准,以推动精准治疗策略的优化与实施。

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