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T细胞淋巴瘤临床诊疗及耐药机制研究进展

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摘要　T细胞淋巴瘤(T-cell lymphoma, TCL)是具有高度异质性和侵袭性的非霍奇金淋巴瘤亚型之一。近年来, 随着精准医学、单细胞测序和多组学分析的发展, T细胞淋巴瘤在诊断、分期及治疗方面的研究取得了显著进展。该文综述了T细胞淋巴瘤的流行病学、诊断、临床治疗及耐药机制, 特别是外周T细胞淋巴瘤、结外NK/T细胞淋巴瘤和其他少见亚型的研究进展。此外, 深入探讨了T细胞淋巴瘤的耐药机制, 包括多药耐药性、肿瘤微环境与免疫逃逸及信号通路异常激活。未来, 随着新兴技术的应用和靶向药物的研发, T细胞淋巴瘤患者的临床预后有望得到进一步改善。

关键词　T细胞淋巴瘤; 临床诊疗; 靶向治疗; 耐药机制

Research Progress on Clinical Diagnosis, Treatment, and Drug Resistance Mechanisms of T-Cell Lymphoma

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Abstract　TCL (T-cell lymphoma) is a subtype of non-Hodgkin lymphoma characterized by high heterogeneity and aggressiveness. In recent years, with the advancements in precision medicine, single-cell sequencing, and multi-omics analysis, significant progress has been made in understanding the diagnosis, staging, and treatment strategies for T-cell lymphoma. This paper reviews the epidemiology, diagnosis, clinical treatment, and drug resistance mechanisms of T-cell lymphoma, with a focus on PTCL (peripheral T-cell lymphoma), ENKTL (extranodal natural killer T-cell lymphoma), and other rare subtypes. Additionally, it explores the mechanisms of drug resistance in T-cell lymphoma, including multidrug resistance, tumor microenvironment and immune evasion, and the abnor-

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mal activation of signaling pathways. The integration of emerging technologies and the development of targeted therapies are expected to further improve the clinical outcomes for T-cell lymphoma patients.

Keywords T-cell lymphoma; clinical diagnosis and treatment; targeted therapy; drug resistance mechanism

淋巴瘤是起源于淋巴造血组织的恶性肿瘤, 主要分为非霍奇金淋巴瘤(non-Hodgkin lymphoma, NHL)和霍奇金淋巴瘤(Hodgkin lymphoma, HL)两大类。非霍奇金淋巴瘤是淋巴瘤的主要类型, 约占所有淋巴瘤的90%, 其病理类型多样, 侵袭性较高[1]; 而霍奇金淋巴瘤相对少见, 可分为结节性淋巴细胞为主型HL(nodular lymphocyte predominant Hodgkin lymphoma, NLPHL)和经典型HL(classic Hodgkin lymphoma, cHL)。cHL约占HL的90%, 特征为Reed-Sternberg细胞与异质性非肿瘤炎性细胞混合存在, 有4种组织学亚型, 即结节硬化型、富于淋巴细胞型、混合细胞型和淋巴细胞消减型[2-3]。T细胞淋巴瘤(T-cell lymphoma, TCL)是NHL的常见亚型, 约占所有非霍奇金淋巴瘤的12%, 以高度侵袭性和显著异质性为特征[4]。TCL病理亚型繁多, 不同亚型的分子遗传学、临床表现及生存预后各异[5]。相较于2017年第4版世界卫生组织(World Health Organization, WHO)淋巴瘤分类, 2022年第5版WHO造血与淋巴组织肿瘤分类(The 5th Edition of the WHO Classification of Haematolymphoid Tumors, WHO-HAEM5)中更加重视基因表达谱(gene expression profiling, GEP)特征在区分不同亚型中的作用[6]。其中, 外周T细胞淋巴瘤–非特指型(peripheral T-cell lymphoma, not otherwise specified, PTCL-NOS)是最常见的TCL亚型, 其次是间变性大细胞淋巴瘤(anaplastic large cell lymphoma, ALCL)和血管免疫母细胞型滤泡辅助性T细胞淋巴瘤(nodal T-follicular helper cell lymphoma, angioimmunoblastic-type, nTFHL-AI)[7], 而结外NK/T细胞淋巴瘤(extranodal natural killer T-cell lymphoma, ENKTL)是一种具有高度侵袭性且较罕见的TCL, 但其发病有显著的地域差异性, 发病率在我国居TCL亚型前列[8]。

过去十年间, 精准医学的出现加深了人们对TCL的生物学、分子亚型和遗传景观的理解; 基础和转化研究的进展为TCL的治疗提供了更多的治疗选择。随着单细胞测序、多组学分析、人工智能技术等手段的成熟发展与广泛应用, TCL致病机制和临床诊治方面的科学研究取得了日新月异的进展。本文将从TCL的诊断、临床治疗及耐药分子机制三个方面, 对其最新研究进展进行综述。

1 流行病学

1.1 外周T细胞淋巴瘤

PTCL起源于胸腺后成熟T细胞或NK/T细胞。在中国的所有NHL病例中, 25%~30%为PTCL, 高于欧洲和美国国家(10%~15%)[9]。PTCL-NOS是最常见的PTCL亚型, 至少占PTCL的25%。该亚型多见于成年患者, 中位发病年龄为60岁, 以男性为主。亚洲的PCTL-NOS发病率(22%)稍低于欧洲和北美(34%)[10-11]。nTFHL-AI仅占所有NHL病例的1%~2%, 但占每年新诊断的TCL病例的近20%[12]。该亚型以中老年人为主, 中位诊断年龄为65岁, 且没有明显的性别差异[13]。nTFHL-AI的地域分布与ENKTL相反, 在欧洲发病率(29%)高于亚洲(18%)[14]。nTFHL-AI已被发现与Epstein-Barr病毒(Epstein-Barr virus, EBV)有着错综复杂的关系, 但其具体的致病机制仍未被完全阐明[15]。ALCL是一类CD30阳性的成熟T细胞淋巴瘤, 尽管在形态学和免疫表型具有一致性, 但其临床和遗传特征呈现高度异质性[16]。目前, 所有类型的ALCL约占TCL的15%[10], 占所有NHL的3%~5%[17]。其中, ALK阳性ALCL主要发生在年轻人中, 男性发病率略高; 该亚型进展迅速, 诊断时通常处于疾病晚期阶段, 常表现出淋巴结肿大和全身系统性症状[18-19]。相比之下, ALK阴性ALCL患者年龄多在40~65岁之间, 男性发病率略高于女性(比值为1.5:1)[20], 约50%的病例显示淋巴结受累, 而结外受累较少见[21]。

1.2 结外NK/T细胞淋巴瘤

ENKTL是一种相对罕见且具有高度侵袭性的非霍奇金淋巴瘤, 也与EBV感染密切相关。其发病率存在显著的地域性差异, 欧美国家少见, 亚洲及拉丁美洲高发, 是我国最常见的TCL亚型[22-24]。多数患者为成年人, 年龄多在46~60岁。根据原发病灶的不同部位, ENKTL可分为上呼吸消化道原发型(upper aerodigestive tract, UAT-ENKTL)和非上呼吸消化道原发型(non-upper aerodigestive tract, NUAT-ENK-

TL)。UAT-ENKTL主要发生于鼻腔及鼻旁区域(如鼻咽、鼻旁窦、韦氏环和口咽), 占ENKTL的80% 以上; 而NUAT-ENKTL主要累及皮肤、胃肠道、睾丸、肝、肺等部位, 仅占ENKTL的10%~20%, 但恶性程度更高, 患者预后较差[25]。

1.3 其他TCL亚型

T淋巴母细胞淋巴瘤(T-lymphoblastic cell lymphoma, T-LBL)起源于未成熟前体T淋巴细胞, 侵袭性强, 恶性程度高。T-LBL的年发病率为1/100 000~5/100 000, 占成人NHL的3%~4%, 在儿童NHL的占比高达40%, 亚洲的发病率亦较欧美高, 在我国等东亚国家较为常见。其发病与电离辐射以及嗜淋巴细胞病毒(HIV、HTLV-1、HHV-8、HCV)的感染相关[26]。

肝脾T细胞淋巴瘤(hepatosplenic T-cell lymphoma, HSTCL)是PTCL的一种罕见亚型, 于1981年首次被发现并描述[27], 占所有PTCL病例的比例不足5%, 全球发病率约为1%[10]。HSTCL在欧美发病率较高, 而其他国家罕见[28]。

肠道T细胞和NK细胞淋巴增殖性疾病和淋巴瘤(intestinal T-cell and NK-cell lymphoid proliferations and lymphomas)的发病率尚无明确统计, 其中发病率最高的为肠病相关T细胞淋巴瘤(enteropathy-associated T-cell lymphoma, EATL), 但EATL本身十分罕见, 约占所有PTCL的5%[29]。EATL的年龄多在50~61岁, 男性发病率略高[29]。

原发性皮肤T细胞淋巴瘤(primary cutaneous T-cell lymphomas, CTCL)是具有T细胞表型的淋巴瘤, 其特征是在诊断时没有皮肤外病灶浸润, 且在疾病发展的过程中通常局限于皮肤, 晚期可能发生皮外扩散。蕈样肉芽肿(mycosis fungoides, MF)是最常见的皮肤T细胞淋巴瘤亚型, 约占皮肤T细胞淋巴瘤的60%[30], 仅占所有NHL的4%, 诊断的年龄多在50~60岁[31], 其次常见的是原发性皮肤CD30阳性T细胞淋巴增殖性疾病[32], 其余皮肤T细胞淋巴瘤则更为罕见。

2 TCL临床诊断特征

淋巴瘤的传统诊断方法主要依靠患者的临床表现、实验室检查、影像学检查、组织病理学检查和分子病理学检查等信息。然而, 由于其复杂性和异质性, 即使是血液病理专家也面临一定的诊断困难。人工智能的发展为TCL的精准诊疗以及高效服务提供了可能, 有助于降低TCL亚型的误诊率并提高临床效率。

2.1 PTCL

PTCL的诊断应通过切除或切开活检收集足够的组织, 以进行免疫表型分析和流式细胞分析。免疫组化标志物包括T细胞标志物(CD3、CD2、CD5、CD7、CD4、CD8)、滤泡辅助性T细胞亚型标志物(CD10、BCL6、PD1/CD279、ICOS、CXCL13)、CD30、ALK、CD56、TCRβ、TCRδ、Ki67和EBV编码区(Epstein-Barr virus-encoded RNA, EBER)原位杂交[33]。诊断时, PTCL患者普遍存在淋巴结受累, 并常伴有结外器官的累及, 包括骨髓(22%)、肝脏、脾脏和皮肤。PTCL患者通常在确诊时即处于晚期, 约70%的患者国际预后指数(international prognostic index, IPI)评分为中至高危[34]。

PTCL-NOS作为一种排他性诊断, 展现了广泛的细胞和分子多样性[35]。基因表达谱分析推动了亚型的重新归类, 将部分病例划分为nTFHL-AI、ALCL或ENKTL[6,36]。

组织病理学检查也是nTFHL-AI的诊断基础, 这一亚型的典型特点是CD30的表达[37]。nTFHL-AI具有3种重叠的组织学模式(主要为II和III)[38]。尽管诊断精度有所提升, 但由于肿瘤性滤泡辅助性T细胞(follicular helper T cells, TFH)的多态性以及肿瘤细胞比例差异性等因素, nTFHL-AI的诊断仍然具有挑战性。鉴于nTFHL-AI的复杂性和异质性, 需整合临床病史、形态学和免疫表型结果以及分子/遗传分析, 来进一步优化其分类与治疗。

ALCL的诊断依赖CD30、T细胞抗原和ALK的免疫组织化学染色[39]。ALK^+ ALCL通常容易诊断, 且预后较好; 而ALK^- ALCL这一亚型因缺乏分子标志物(如ALK)协助诊断, 与其他淋巴瘤亚型的分子标志物存在重叠, 例如与PTCL-NOS的区分较为困难, 从而增加了诊断的复杂性[40]。随着GEP等技术的发展, ALCL的诊断分类有望进一步细化, 但建立一个准确高效的诊断体系仍然任重道远。

2.2 ENKTL

组织病理学检查是ENKTL的主要诊断方式, 包括形态学、免疫组化、流式细胞术和T细胞受体(T cell receptor, TCR)重排检查。ENKTL病理诊断主要包括胞质CD3ε、CD2、CD5、CD56、CD4、CD8、CD20、PAX5、TIA-1、granzyme B、Ki-67等免疫组

化标志物以及EBER原位杂交等[41-42]。此外, EBV感染是ENKTL诊断的必要条件[43]。由于肿瘤组织易坏死, 活检能够提高诊断的准确性。近年来, ENKTL精准诊断的体系在多组学、人工智能等技术的发展下不断完善细化。例如有研究者开发了基于人工智能算法和鼻咽部核磁共振成像的诊断和预后系统, 为临床上鼻咽部肿物的鉴别诊断以及ENKTL患者的精准分层提供了更多依据, 并提升了早期诊断的精准性[44]。

过去十年间TCL领域的研究工作, 初步建立了不同病理亚型的分型诊断体系。未来需进一步融合新兴技术、整合各种病理亚型的TCL特点, 开发精准高效的人工智能辅助诊断系统。

3 临床分期与风险分层

3.1 PTCL

目前, 几种结合实验室和临床特征的预后评分广泛应用于PTCL的临床实践, 包括经典的IPI、年龄调整后的IPI(age adjusted IPl, aaIPI), 以及来自国际T细胞淋巴瘤项目的T细胞评分(包括年龄、分期、白蛋白和中性粒细胞计数绝对值)[10]等。既往相关研究显示, PTCL中TP53/CDKN2A突变、组蛋白突变修饰基因突变的患者预后较差[45-46]。此外, 研究者通过全外显子组测序(whole exome sequencing, WES)、靶向测序和RNA测序(RNA sequencing, RNA-seq)等技术描绘了一个全面的PTCL突变基因组图谱, 并根据遗传特征、生物学改变和治疗反应建立了分子分层, 提出了4种不同的PTCL分子亚群[47], 为PTCL患者的个性化治疗提供了理论依据。

ALCL有四种不同的亚型, 即ALK$^-$ ALCL、ALK$^+$ ALCL、乳房植入物相关ALCL和皮肤ALCL。对于ALK$^+$ ALCL患者, ALK表达阳性以及基线较低的IPI评分与更好的预后相关[48]。研究显示, 使用含蒽环类药物的方案治疗后, ALK$^+$患者预后优于ALK$^-$患者, 前者的5年总生存率(overall survival, OS)为79%, 后者仅为46%[49]。ALK$^-$ ALCL的预后通常较差, 但DUSP22重排可能与较好的预后相关, 有这一重排特征的ALK$^-$ ALCL患者5年总生存率与ALK$^+$ ALCL相当[50]。乳房植入物相关ALCL通常局限于植入物浅表或其周围, 肿瘤及异物完全切除后的预后良好, 预期5年OS率和无进展生存(progression free survival, PFS)率均为100%[51]。

针对nTFHL-AI, 研究表明高IPI评分和PTCL-U(peripheral T-cell lymphoma unspecified)评分[年龄、美国东部肿瘤协作组(eastern cooperative oncology group, ECOG)评分、乳酸脱氢酶(lactate dehydrogenase, LDH)水平、骨髓受累][52], 以及低血小板计数值, 均与不良预后相关[13-14,53]。EBV的存在与预后之间的关系存在争议: 一项评估利妥昔单抗联合CHOP(环磷酰胺、多柔比星、长春新碱和泼尼松)疗效的研究显示, EBV-DNA高水平患者的PFS较短[54]; 但也有研究表明, EBV阳性细胞的存在并未改变预后[13]。有研究团队基于34个与临床结果相关的基因提出3种与肿瘤微环境有关的基因表达模式, 并验证其与预后的关系, 发现B细胞相关表达模式与较好的预后相关[36]。

3.2 ENKTL

ENKTL目前仍以Ann Arbor分期为主, 并结合Lugano分期进行修正。然而, ENKTL主要原发部位多在结外, 淋巴结侵犯相对少见且常伴广泛周围组织侵袭; 采用Ann Arbor分期时, 超过80%的病例被归类为早期, 但这部分患者的治疗反应和预后却不理想, 说明Ann Arbor分期难以对ENKTL进行精准的分期[55-59]。有研究团队针对这一问题构建了中国南方肿瘤临床研究协会和亚洲淋巴瘤协作组分期系统, 简称CA分期[60]。此外, 在目前以门冬酰胺酶为基础的化疗时代中, 临床广泛应用了针对ENKTL的多种预后模型, 如ENKTL预后指数PINK(prognostic index of natural killer lymphoma)/PINK-E和列线图简化风险指数(nomogram-revised risk index, NRI), 用于患者的风险管理。研究者通过分析国际多中心ENKTL患者数据, 构建了PINK预后分层模型, 该模型结合了年龄、Ann Arbor分期、是否远处淋巴结受累、有无鼻外病灶等因素[61]; 并在此基础上, 通过整合血浆EBV-DNA水平衍生出PINK-E模型。两种模型可有效区分不同风险分层患者的预后, 并被美国国立综合癌症网络(national comprehensive cancer network, NCCN)指南所采纳。而NRI模型则综合了ECOG评分、LDH水平、Ann Arbor分期、原发肿瘤侵犯(primary tumor invasion, PTI)和年龄5个独立预后不良因素, 将患者分为早期低危、中低危、中高危和高危4个风险组[62-63]。

研究显示, ENKTL是一种以抑癌基因和表观遗传学异常为主导的疾病[64]。例如, 利用全基因

组水平的基因变异信息和关联分析等技术发现，*HLA-DPB1*、*IL18RAP*和*HLA-DRB1*是中国汉族人群罹患ENKTL的易感基因[65-66]。有研究团队对128例ENKTL肿瘤样本进行基因组测序(whole genome sequencing, WGS)，提出基于分子遗传学特征的三种亚型[64]——TSIM、MB和HEA亚型，各亚型与免疫活性、基质成分等特征及临床结局相关(例如，TSIM亚型表现为较高的免疫浸润活性，而MB亚型则与基质成分丰富相关)，为ENKTL靶向治疗提供潜在思路。此外，有研究团队采用单核苷酸多态性(single nucleotide polymorphism, SNP)芯片和LASSO回归模型技术，联合临床指标共同构建了一个7联SNP分子标签[67]，用于鉴别从联合放化疗中获益的早期高危患者，优化I期ENKTL患者的分层治疗模式。另一项研究通过液体活检结合高通量甲基化测序，开发了一个7联循环肿瘤DNA(circulating tumor DNA, ctDNA)甲基化诊断标签[68]，并据此构建出新型PINK-C预后模型，为ENKTL的预后评估提供了新的风险分层工具。近来，有研究团队根据127例初治ENKTL患者以及36例ENKTL复发/难治患者的全基因组测序和全外显子测序数据，构建了一套新的ENKTL分子分型系统(C0-C4)[69]，为ENKTL精准临床诊疗提供指导。总体而言，多组学分型相关预后模型在指导个体化精准治疗方面展现优势，但仍需经过大规模临床队列的验证以确定其临床应用价值。

3.3 其他TCL亚型

T-LBL具有恶性程度高、复发率较高的特点[70]。通过miRNA标签筛选，有研究团队识别了第一次完全缓解后适合造血干细胞移植(hematopoietic stem cell transplantation, HSCT)巩固治疗的高危T-LBL患者，其5年总生存率(46%)明显优于未进行HSCT的高危患者(29%)[71]。针对T-LBL患者诱导治疗方案的选择，研究者通过全基因表达谱构建预测模型[72]，并发现模型评分>154.2分的T-LBL患者更适合BFM(长春新碱+柔红霉素+L-门冬酰胺酶+泼尼松)化疗方案，而评分≤154.2分的T-LBL患者在hyper-CVAD(hyper-CVAD方案由A、B方案组成，A方案化疗药物包括：环磷酰胺、多柔比星、长春新碱、地塞米松；B方案化疗药物包括：甲氨蝶呤、阿糖胞苷。两种方案交替使用，都为4个疗程)化疗方案中获益更多。另一研究通过微阵列分析构建由4个CpG组成的分子标签[73]，成功区分出复发风险高的T-LBL患者与低风险患者，并协助确定最能从强化化疗和/或序贯造血干细胞移植获益的患者亚组。

其他TCL亚型，如CTCL、肠道NK/T细胞淋巴瘤、HSTCL等，每种亚型都有其独特的生物学特性，因此需要针对不同亚型进行深入学习。未来研究重点在于完善精准诊疗体系，推动患者早诊早治，实现长期生存目标。

4 TCL的治疗

4.1 TCL的一线治疗

对于PTCL患者，基于蒽环类药物的化疗方案[如CHOP(环磷酰胺、多柔比星、长春新碱和泼尼松)、CHOP+依托泊苷或DA-EPOCH(依托泊苷、泼尼松、长春新碱、环磷酰胺和多柔比星)]是最常用的一线治疗方案。ALK阳性ALCL经含蒽环类药物的方案治疗后的预后明显优于其他亚型，其5年无失败生存率和总生存率分别为60%和70%[10,74]。一项使用罗米地辛联合CHOP(Ro-CHOP)对比CHOP方案一线治疗PTCL的III期随机对照研究结果显示：中位随访时间27.5个月，尽管Ro-CHOP联合方案较CHOP并未增加≥3级治疗相关不良反应(treatment-related adverse event, TRAE)，但未能改善初治PTCL患者的PFS或OS[75]。一项III期随机试验(ECHELON-2研究)表明，对于初治CD30阳性PTCL(CD30表达≥10%的细胞)患者，维布妥昔单抗(brentuximab vedotin, BV)联合CHP(环磷酰胺、多柔比星和泼尼松)的疗效优于CHOP，可显著改善患者的PFS和OS[76]。基于该研究，维布妥昔单抗联合CHP被美国食品药品监督管理局(Food and Drug Administration, FDA)批准用于系统性ALCL或其他$CD30^+$ PTCL亚型患者的一线治疗方案。ECHELON-2研究的亚组分析评估了BV-CHP后巩固性自体造血干细胞移植(autologous stem cell transplantation, ASCT)对治疗结束时达到完全缓解(complete response, CR)的患者的影响，发现接受ASCT患者有较大PFS获益(5年PFS 65% *vs* 46%)[77]。NCCN指南推荐初次治疗后达到CR或部分缓解(partial response, PR)且适合移植的淋巴结侵袭性PTCL患者可考虑ASCT，仍目前仍缺乏大样本随机对照研究支持。目前多项针对初治TCL患者的临床试验也正在开展(表1)。

ENKTL患者对含蒽环类药物的方案反应不佳，NCCN指南推荐含左旋门冬酰胺酶或培门冬酶为基

础的化疗方案, 包括P-GemOx(培门冬酶、吉西他滨、奥沙利铂)、DDGP(地塞米松、顺铂、吉西他滨、培门冬酶)[78]、GELAD(地塞米松、依托泊苷、吉西他滨、培门冬酶)[79]、剂量调整的SMILE(地塞米松、甲氨蝶呤、异环磷酰胺、L-门冬酰胺酶、依托泊苷)和AspaMetDex方案(L-门冬酰胺酶、甲氨蝶呤、地塞米松)[80]。I期~II期ENKTL需要进行风险分层治疗, I期无危险因素(年龄<60岁, ECOG 0~1分, LDH正常, I期无原发肿瘤局部广泛侵犯), 单纯放疗即可取得较好的效果。I期伴有危险因素及II期, 联合放化疗是标准治疗, 单纯放疗或单纯化疗都存在较高的进展和复发风险。III~IV期ENKTL患者以化疗为主, 残存病灶可考虑局部加放疗, 可选用含门冬酰胺酶的化疗方案或推荐参与临床试验[81]。一项前瞻性、随机对照的III期研究对比了无静脉输注ESA方案(依托泊苷、地塞米松、培门冬酶)与MESA方案(甲氨蝶呤、ESA)联合夹心放疗治疗早期ENKTL患者的疗效及安全性, 研究结果表明ESA方案与MESA方案相比, 总体疗效具有非劣效性, 但3级以上TRAE发生率显著低于MESA组(34% *vs* 66%)[82]。另一项探索信迪利单抗联合安罗替尼和培门冬酶的一线治疗早期ENKTL患者的研究结果显示: 6程治疗后CR率和客观缓解率(objective response rate, ORR)均为88%, 2年PFS和OS率分别为88%和98%[83]。针对晚期患者, 既往研究初步表明程序性死亡受体1(programmed death-1, PD-1)单抗联合P-GEMOX方案一线治疗晚期ENKTL患者疗效良好(ORR和CR率分别为100%和89%)[84]; 基于此, 一项前瞻性、单臂、多中心II期试验SPIRIT研究进一步探索了信迪利单抗联合P-GemOx方案一线治疗晚期ENKTL患者的疗效及安全性, 结果显示CR率为85%, ORR为100%, 2年PFS率为64%, 2年无病生存(disease-free survival, DFS)率为72%, 3年OS率为76%, 整体疗效及安全性良好, 提示PD-1单抗联合P-GemOx的免疫化疗可作为晚期ENKTL一线治疗的新方案[85]。

对于其他TCL亚型, 不同类型也有各自针对性

表1 初治TCL中正在进行的临床试验

Table 1 Ongoing clinical trials in newly diagnosed TCL

NCT编号 NCT number	研究标题 Study title	治疗 Interventions	阶段 Phase
NCT02223208	Romidepsin in combination with CHOEP as first line treatment before hematopoietic stem cell transplantation in young patients with nodal peripheral T-cell lymphomas: a phase 1/2 study	Drug: romidepsin, doxorubicin, vincristin, cyclophosphamide, etoposide, prednisone	Phase I/II
NCT05896813	CMOP regimen and chidamide in the treatment of newly diagnosed peripheral T-cell lymphoma	Drug: chidamide, cyclophosphamide, mitoxantrone hydrochloride liposome, vincristine, prednisone	Phase II
NCT03113500	Brentuximab vedotin and combination chemotherapy in treating patients with CD30-positive peripheral T-cell lymphoma	Drug: brentuximab vedotin, cyclophosphamide, doxorubicin	Phase II
NCT02232516	Romidepsin and lenalidomide in treating patients with previously untreated peripheral T-cell lymphoma	Drug: romidepsin, lenalidomide	Phase II
NCT04127227	Sintilimab with P-GemOx regimen for newly diagnosed advanced extranodal natural killer/T-cell lymphoma, nasal type	Drug: sintilimab, pegaspargase, gemcitabine, oxaliplatin	Phase II

的治疗策略。T-LBL一线诱导治疗以多药联合的治疗方案为主，常用的诱导方案为VDLP(泼尼松、长春新碱、柔红霉素、培门冬酶)和Hyper-CVAD A/B方案(环磷酰胺、长春新碱、阿霉素、地塞米松与甲氨蝶呤、阿糖胞苷交替使用)等[86]。HSTCL目前尚无标准治疗方案。NCCN指南推荐可使用ICE(异环磷酰胺、卡铂、依托泊苷)或IVAC(甲磺酸钠、依托泊苷和阿糖胞苷)等方案进行强化诱导后对病情缓解的患者进行早期异基因干细胞移植[87]。

4.2 TCL的靶向治疗

复发或难治性TCL患者目前尚无标准疗法，其生存结局较差，亟需更为有效的治疗方案来提高患者的总体疗效。随着高通量测序技术在TCL中的广泛应用，新型治疗靶点及靶向药物正不断涌现，目前正在开发的新药种类主要包括靶向细胞表面抗原的抗体、免疫检查点抑制剂、靶向表观遗传学改变的药物和信号通路抑制剂等，多项新药临床试验也正在开展(表2)。

4.2.1 *靶向肿瘤细胞表面抗原的抗体* 多项研究证实TCL肿瘤细胞异常表达多种细胞表面抗原分子(包括CD30、CD38和CD25等)[88-89]，这些分子参与调控免疫细胞的增殖、分化及死亡过程，其异常表达在TCL的发生发展中发挥着重要作用。

CD30表达于活化的淋巴细胞中，可介导多条信号转导通路从而调控细胞生长、增殖和凋亡。维布妥昔单抗(brentuximab vedotin, BV)是一种抗体药物偶联(antibody-drug conjugate, ADC)药物，由靶向CD30的单克隆抗体和一种细胞毒性药物MMAE(微管抑制剂)通过共价键相连[90]。既往研究发现CD30在ALCL中普遍表达，维布妥昔单抗在R/R ALCL中

表2 复发/难治性TCL中正在进行的新药临床试验

Table 2 Ongoing clinical trials of new drugs in relapsed/refractory TCL

NCT编号 NCT number	研究标题 Study title	治疗 Interventions	阶段 Phase	药物靶点 Drug target
NCT05321147	A phase 2 study of single agent brentuximab vedotin in relapsed/refractory CD30 low (<10%) mature TCL (T cell lymphoma)	Drug: brentuximab vedotin	Phase II	Anti-CD30 monoclonal antibody
NCT04763616	Study of isatuximab and cemiplimab in relapsed or refractory natural killer/T-cell lymphoid malignancy (ICING)	Drug: isatuximab; cemiplimab	Phase II	Anti-CD38 monoclonal antibody; anti-PD1 antibody
NCT04337593	Combination of basiliximab and pegaspargase in the treatment of ENKTL	Drug: basiliximab; pegaspargase	Phase II	Anti-CD25 monoclonal antibody
NCT04414163	A study of IMC-001 in subjects with relapsed or refractory extranodal NK/T cell lymphoma, nasal type	Drug: IMC-001	Phase II	Anti-PD1 antibody
NCT04296786	Sintilimab plus chidamide in the treatment of relapsed and refractory cutaneous T-cell lymphoma: a multicenter phase 2 study	Drug: sintilimab; chidamide	Phase II	Anti-PD1 antibody; HDACi
NCT04447027	Romidepsin, CC-486 (5-azacitidine), dexamethasone, and lenalidomide (RAdR) for relapsed/refractory T-cell malignancies	Drug: romidepsin; lenalidomide; CC-486; dexamethasone	Phase II	DNMT inhibitor; HDACi
NCT02974647	Study of ruxolitinib in relapsed or refractory T or NK cell lymphoma	Drug: ruxolitinib	Phase II	JAK1/2 inhibitor
NCT03598959	Tofacitinib combined with chidamide in R/R ENKTL	Drug: tofacitinib; chidamide	Phase II	JAK1/3 inhibitor; HDACi
NCT05269940	A study to evaluate activity, safety and tolerability of ZX-101A in relapsed/refractory hematological malignancies	Drug: ZX-101A	Phase I/II	PI3Kδ/γ dual target inhibitor
NCT04774068	Romidepsin and parsaclisib for the treatment of relapsed or refractory T-cell lymphomas	Drug: parsaclisib; romidepsin	Phase I	PI3Kδ inhibitor; DNMT inhibitor

已证明其安全性和疗效, 治疗结束后的中位随访时间为58.4个月, 仍有66%的患者保持完全缓解且ALK阴性和ALK阳性ALCL患者的缓解率相似, 接受维布妥昔单抗治疗后达到CR的患者5年OS率和5年PFS率分别为79%和48%, 在不联合移植巩固的情况下也能获得长期疾病控制[91]。维布妥昔单抗单药已获得FDA批准用于治疗R/R系统性ALCL。一项正在开展的II期研究评估了维布妥昔单抗吉西他滨联合治疗R/R CD30$^+$(≥5%) PTCL患者的疗效及安全性, 结果显示ORR为47%, 且缓解患者的缓解持续时间(duration of response, DOR)可达15个月[92]。

CD38是表达于免疫细胞中的一种II型跨膜糖蛋白, 参与细胞黏附与跨膜信号转导过程, 有研究显示ENKTL患者的肿瘤细胞高表达CD38[93]。达雷妥尤单抗(daratumumab)是全球以及国内首个获批的靶向CD38的mAb, 一项纳入32例复发难治性ENKTL患者的II期单臂临床研究显示, 达雷妥尤单抗单药治疗的疗效有限, ORR仅为25%[94]。有研究提示靶向CD38的mAb可增强对免疫检查点抑制剂的治疗反应[95], 提示两药联用在未来可能更具治疗价值, 在一项探索cemiplimab(PD-1抑制剂)联合isatuximab(CD38单抗)治疗R/R ENKTL的II期研究中, 初步结果报道ORR和CR率分别为65%和43%, 且PD-L1高表达的患者较低表达的患者有更好的疗效[96]。

CD25是高亲和力白细胞介素2受体的α亚基, 存在于活化淋巴细胞的细胞表面, 40%~50%的PTCL患者肿瘤细胞表达CD25[33]。Cami(Camidanlumab tesirine)是一种与细胞毒性吡咯苯二氮卓类二聚体偶联的CD25抗体, 在R/R PTCL患者中显示出良好的缓解(ORR为48%)[97]。E7777是一种由白喉毒素和人IL-2组成的重组融合蛋白, 一项使用E7777治疗R/R CD25$^+$(≥20%) PTCL的II期研究结果显示ORR为41%, 同时不良反应可控[98], 未来可能为复发难治性TCL患者提供一种新的治疗选择。

此外, CD52、CD40、CCR4、B7H3和CD70也被认为可能是TCL潜在的治疗靶点, 针对上述靶点, 许多新药也正不断研发并应用于TCL的治疗中, 例如靶向CD52的mAb阿仑单抗(alemtuzumab)[99]、靶向CD25的mAb巴利昔单抗(basiliximab)[100]等, 相关临床试验正在开展, 未来将为TCL患者提供更多的治疗选择。

4.2.2 *免疫检查点抑制剂* 免疫检查点在肿瘤微环境免疫耐受性的发展和维持中起着关键作用, 阻断免疫检查点激活肿瘤反应性T细胞并产生抗肿瘤效应[101]。目前已有多种免疫检查点抑制剂在TCL治疗中应用, 包括抗PD-1单抗如帕博利珠单抗、信迪利单抗、替雷利珠单抗、特瑞普利单抗等, 以及抗PD-L1单抗如舒格利单抗和阿维单抗。

ORIENT-4研究是一项探索信迪利单抗单药治疗复发/难治性ENKTL患者的II期单臂临床试验[102], 结果显示在28名患者中, ORR为75%, 2年OS率可达79%。另一项使用替雷利珠单抗单药治疗R/R ENKTL患者的II期研究结果显示, 在纳入的22例ENKTL患者中, ORR和CR率仅为32%和18%, 可能由于该研究所纳入的患者基线肿瘤负荷高所致[103]。抗PD-L1单抗舒格利单抗治疗80名复发/难治性ENKTL患者的单臂II期临床试验显示ORR和CR率分别为46%和30%, 1年和2年OS率分别为69%和55%[104]。在KIM等[105]进行的一项使用阿维单抗单药治疗R/R ENKTL的II期研究中, CR率和ORR分别为24%和38%, 实现CR的5名患者均高表达PD-L1。此外, 有研究报道EBV驱动的潜伏膜蛋白(latent membrane protein 1, LMP1)通过核因子κB(nuclear factor-κB, NF-κB)信号通路可增加PD-L1的表达水平, STAT3激活也被发现可以增加PD-L1的表达水平[106], 鉴于此, 使用PD-L1抑制剂与其他药物(如STAT3抑制剂和EBV靶向的细胞毒性T淋巴细胞)联用治疗ENKTL或许是未来值得探索的一个方向。

4.2.3 *靶向表观遗传学改变的药物* 表观遗传学异常在TCL的发生发展中具有重要作用, 有研究表明在多种TCL亚型中存在TET2、IDH2、DNMT3A等表观遗传学修饰和调节基因异常, 其引起的表观遗传学信号变化与抑癌基因沉默相关[107]。此外, 表观遗传学介质EZH2(zeste同源物2的增强子)的异常表达或突变也可导致抑癌基因转录沉默。

阿扎胞苷和地西他滨是DNA甲基转移酶(DNA methyltransferase, DNMT)抑制剂, 其针对R/R TCL患者的多项研究正在开展。一项使用阿扎胞苷治疗12例R/R nTFHL-AI患者的研究结果显示ORR和CR率分别为75%和50%, 且所有缓解患者均检测到携带TET2突变[108]。Valemetostat是一种强效的EZH1/2抑制剂, 在日本获批用于治疗复发/难治T细胞白血病/淋巴瘤成人患者。在R/R PTCL的一项全球性单

臂II期临床试验(VALENTINE-PTCL01)中, 持续性口服valemetostat(200 mg/d)耐受性良好, ORR和CR率分别为44%和1%, 中位DOR为11.9个月, 并且各种PTCL亚型均有反应。中位PFS和OS分别为5.5个月和17.0个月[109]。

组蛋白去乙酰化酶抑制剂(histone deacetylase inhibitors, HDACi)通过使肿瘤抑制基因的组蛋白去乙酰化而发挥细胞毒效应[110]。西达苯胺是HDAC1、2、3和10的选择性抑制剂[111]。既往一项回顾性研究提示西达苯胺联合化疗可为R/R PTCL患者带来显著的PFS获益[112]。一项多中心II期临床试验, 评估了西达本胺和阿扎胞苷联合或不联合GemOx(吉西他滨、奥沙利铂)方案治疗R/R PTCL患者的疗效, 结果显示在30名可评效的患者中, 最佳ORR为53.3%, 中位PFS和中位OS分别为7.1个月和8.7个月, nTFHL-AI患者的整体疗效高于非nTFHL-AI患者[113]。另一项使用西达苯胺联合PD-1单抗治疗R/R ENKTL患者的Ib/II期研究展示出良好疗效, ORR和CR率分别为59.5%, 中位随访时间38.7个月, 中位PFS和中位OS分别为23.2个月和32.9个月[114]。

4.2.4 信号通路抑制剂 GEP提示PTCL患者中存在JAK/STAT、NF-κB、PI3K/Akt/mTOR和PDGFR等信号通路的异常激活[115], 目前已有多种新药针对这些通路进行相应的靶向治疗。

JAK/STAT信号通路在包括T细胞恶性肿瘤在内的多种血液系统恶性肿瘤的发生发展中具有重要作用[116]。应用芦可替尼(JAK1和JAK2抑制剂)或cerdulatinib(泛JAK和SYK抑制剂)的临床研究显示, 在复发或难治性外周T细胞淋巴瘤患者中, 阻断JAK-STAT信号通路具有良好的抗肿瘤活性[117]。Golidoctinib是一种口服JAK1特异性抑制剂, 一项国际多中心II期临床研究JACKPOT-8使用golidoctinib单药治疗R/R PTCL, 结果显示出良好的抗肿瘤活性, ORR和CR率分别为44%和30%, 中位随访12.5个月, 中位DOR为20.7个月, 在不同亚型中均观察到获益[118], 同时安全性可控。

PI3K/Akt/mTOR通路的异常调控已被证实可促进肿瘤细胞增殖和存活[119]。Duvelisib是一种口服的新型选择性PI3Kδ/γ抑制剂, 一项使用duvelisib治疗R/R PTCL患者的II期PRIMO研究结果显示, ORR和CR率分别为49%和34%, 中位DOR为7.7个月; 其中, PTCL-NOS(ORR 48%)和nTFHL-AI(ORR 67%)亚型患者的生存结局明显优于ALCL患者(ORR 13%)[120]。另一项Ib/IIa期临床试验评估了度维利塞联合罗米地辛(HDACi)在复发/难治性TCL患者中的疗效和安全性, 结果显示ORR为54%, CR率为37%, 中位DOR为12个月, 该I期研究阶段3/4级不良事件(adverse event, AE)发生率(13.6%)显著低于度维利塞单药治疗的患者(40%)[121]。总的来说, PI3K抑制剂在TCL患者中具备良好的抗肿瘤活性, 但考虑到其异构体特异性引起的毒性问题, 未来还需要进一步了解各种基因突变与不同亚型缓解和耐药的相关性, 以做出合理决策。

5 TCL的耐药机制

耐药性是TCL临床治疗失败、患者死亡的最主要原因, 导致患者在接受一线或多线治疗后出现疾病复发或进展。TCL的耐药机制复杂多样, 涉及肿瘤细胞的内在的异质性以及肿瘤微环境(tumor microenvironment, TME)的改变(图1)。

5.1 多药耐药性

多药耐药(multidrug resistance, MDR)表型是TCL的重要耐药机制之一[122], MDR是指对多种结构和功能不相关药物的获得性交叉耐药, ABC(ATP-binding cassette)转运体家族过表达是MDR的关键机制, 尤其是P-糖蛋白(P-glycoprotein, P-gp)的上调导致化疗药物(如阿霉素和长春新碱)被外排出肿瘤细胞, 细胞内药物浓度降低从而引起耐药[123]。ENKTL患者高表达MDR蛋白, 一项研究通过免疫组化检测了45例ENKTL患者P-gp、多药耐药相关蛋白、乳腺癌耐药蛋白和肺耐药蛋白的表达, 结果显示阳性率分别为31%、74%、78%和59%[124]。UNO等[125]发现在EBV感染下, ENKTL肿瘤细胞内ROS的产生会通过STAT1途径增加P-gp的表达水平, ROS清除剂可有效逆转EBV阳性ENKTL中P-gp相关的化疗耐药; 此外, LMP1和/或其他EBV病毒组分也参与P-gp依赖性化疗耐药[126]。

5.2 肿瘤微环境与免疫逃逸

TME内基质细胞与肿瘤细胞之间的相互作用以及可溶性因子的分泌是TCL治疗耐药的促成因素。免疫检查点如PD-1和PD-L1在肿瘤微环境免疫耐受性的发展和维持中起着关键作用, 其传递T细胞活化的抑制信号从而介导免疫逃逸[127]。39%~100%的ENKTL患者表达PD-L1[128], EBV驱动的LMP也可

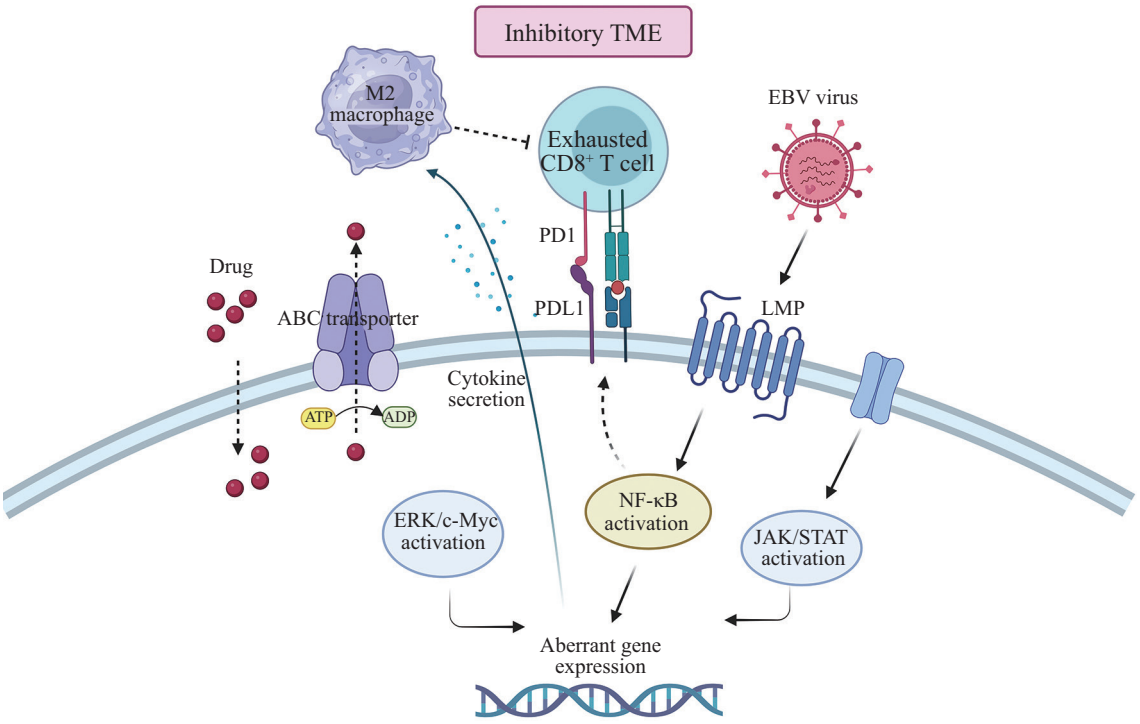

图1 TCL的耐药机制

Fig.1 Mechanisms of drug resistance in TCL

通过NF-κB信号通路增加PD-L1的表达水平，肿瘤细胞的PD-L1表达水平升高与患者的不良预后显著相关[129]。有研究指出PTCL-NOS中GATA3亚组预后相对较差，因其特征的2型辅助T细胞相关细胞因子(包括IL-4、IL-5、IL-10和IL-13)可促进巨噬细胞极化为M2型巨噬细胞，M2型巨噬细胞可通过分泌促血管生成细胞因子促进血管生成，还可分泌IL-10和转化生长因子，以自分泌方式上调巨噬细胞PD-L1的表达，从而抑制T细胞功能产生免疫抑制[130]。总体而言，目前对TCL肿瘤微环境的认识仍处于早期阶段，其介导免疫逃逸及治疗耐药的具体机制有待进一步阐明。

5.3 关键信号通路的异常激活

TCL的耐药性与多种信号通路的异常激活有关，这些信号通路不仅参与肿瘤细胞的增殖和存活，还通过调控药物耐受性基因的表达，直接或间接地促进耐药。NF-κB参与多种淋巴恶性肿瘤的促增殖信号转导，在TCL中，NF-κB通路的持续激活与化疗耐药密切相关[131]。有研究发现，EBV编码的LMP1通过激活MAPK/NF-κB通路上调IL-2Rα表达，从而导致ENKTL对一线化疗药物门冬酰胺酶耐药[100]。针对T淋巴母细胞淋巴瘤/白血病复发耐药问题，相关研究发现溴结构域蛋白BRD2(BET家族成员之一)在化疗抵抗的T-LBL肿瘤组织中表达上调并与不良预后相关，进一步机制研究发现BRD2可通过激活ERK/c-Myc通路，增强T-LBL肿瘤细胞对化疗药物抵抗能力[132]。JAK/STAT信号通路的异常激活是TCL耐药的另一个重要机制，特别是在ENKTL患者中，JAK3、STAT3和STAT5B的突变可能导致该通路的持续激活从而介导免疫化疗耐药[84]。

6 总结与展望

TCL作为一种高度异质性和侵袭性的恶性肿瘤，仍然面临着诊断困难、治疗选择有限和复发率较高等挑战。然而，随着单细胞测序、多组学分析等技术的快速发展，TCL的分子病理机制和临床治疗策略得到了显著的提升。未来的研究应继续深化对TCL发生、发展及耐药机制的探索，同时加快新型靶向药物的开发和临床转化，以期改善TCL患者的预后和生存质量。

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