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评 述 EB病毒发现60周年: 回顾与展望专题

EBV相关NK/T细胞淋巴瘤的研究进展

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摘要 NK/T细胞淋巴瘤(natural killer/T-cell lymphoma, NKTCL)是一种罕见的且侵袭性高的非霍奇金淋巴瘤亚型, 其发病率存在显著的地域差异, 高发于亚洲及拉丁美洲, 与EB病毒(Epstein-Barr virus, EBV)感染密切相关. 近年来, 高通量测序技术的应用揭示了NKTCL异质性的生物学基础和发生发展的分子致病机制, 包括染色体6q21等位基因缺失引起抑癌基因沉默, EB病毒感染及体细胞基因突变导致多条致癌信号通路异常激活, 以及表观遗传学调控异常等. 目前针对NKTCL, 国内外尚无统一的治疗标准, 早期以放疗和化疗综合治疗为主, 而晚期以单纯化疗为主. 晚期及复发难治性患者的预后较差, 亟需探索更多有效的治疗方案, 随着全球新药研发加速演进, NKTCL领域各种新药也层出不穷. 本文就EBV相关NK/T细胞淋巴瘤相关研究进展进行综述.

关键词 NK/T细胞淋巴瘤, EB病毒, 化疗, 放疗, 免疫治疗

NK/T细胞淋巴瘤(natural killer/T-cell lymphoma, NKTCL)是一种罕见且侵袭性高的非霍奇金淋巴瘤(non-Hodgkin lymphoma, NHL), 也是我国最常见的外周T细胞淋巴瘤(peripheral T-cell lymphoma, PTCL)亚型, 与Epstein-Barr病毒(Epstein-Barr virus, EBV)感染密切相关[1~3]. 在病理确诊时, 几乎所有的NKTCL患者中都可以检测到EBV的感染痕迹, 这表明该病毒可能在肿瘤的发生和进展中起到促进作用. NKTCL可根据原发病灶的位置分为上呼吸消化道原发NKTCL(upper aerodigestive tract, UAT-NKTCL)和非上呼吸消化道原发NKTCL(non-upper aerodigestive tract, NUAT-NKTCL). UAT-NKTCL主要发生于鼻腔/鼻旁区域(如鼻咽、鼻旁窦、韦氏环和口咽), 占NKTCL的80%以上; NUAT-NKTCL主要累及皮肤、胃肠道、睾丸、肝、肺等部位, 仅占NKTCL的10%~20%, 但恶性程度较高, 患者预后较差[4]. NKTCL的发病率存在显著地域性差异, 欧美国家少见, 亚洲及拉丁美洲高发, 严重危害我国人民健康. 作为最常见的结外淋巴瘤, NKTCL最常见的发病部位是鼻腔, 主要表现为鼻或面部中线进行性的破坏性病变, 鼻腔肿块引起的鼻塞、

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鼻腔异常分泌物和鼻出血是常见的首发症状.

NK细胞和T细胞源自相同的具有双向分化潜能的淋巴前体细胞[5], 在发育过程中由于表达不同的转录因子而分化为不同的细胞谱系. 大多数NKTCL为NK细胞起源, 未发生T细胞受体基因(T-cell receptor, TCR)的重排; 约40%的NKTCL为T细胞起源, 具有TCR基因重排和TCR蛋白表达的特征[6]. NKTCL分子异质性高, 相关分子致病机制尚未完全阐明; EBV感染可能通过影响细胞的基因表达和免疫逃逸机制, 进一步加剧了NKTCL的侵袭性. 早期NKTCL患者在接受标准放疗及化疗后, 5年总生存期(overall survival, OS)率可达70%~80%[7]; 而晚期以及复发难治性患者的生存结局较差, 标准非蒽环类药物一线治疗后复发的患者中位总OS仅为6个月[8]. 目前, 高通量测序技术已被广泛应用于NKTCL相关研究中, 揭示了NKTCL的分子致病机制和潜在的治疗靶点, 为NKTCL患者提供了更多的治疗选择. 本文综述了目前NKTCL的系列研究, 包括致病机制、诊断、预后和治疗等方面的现状及最新进展, 旨在为探索NKTCL的精准诊疗策略提供新思路.

1 NKTCL的致病机制

目前的研究认为, NKTCL的发生发展包括以下几个主要的致病因素. 其中, EBV感染在NKTCL发生中发挥了关键作用, 通过潜伏感染和特定基因的表达异常促进了肿瘤细胞增殖和免疫逃逸. 此外, NKTCL患者中存在一些发生频率较高的染色体缺失和基因突变, 这些变化导致抑癌基因失活和信号通路异常激活; 表观遗传调控的异常, 如*EZH2*和*BCOR*等基因的异常表达, 也在NKTCL进展中起到了重要作用. 总体而言, 这些发现加深了对NKTCL分子机制的理解, 并为精准治疗提供了新的方向.

1.1 EBV感染

EBV感染在NKTCL的发生发展中发挥重要作用, 肿瘤样本普遍呈现EBV阳性[9], 血清中高水平EBV-DNA拷贝数与肿瘤负荷和不良生存预后密切相关[10]. EBV潜伏感染被认为是EBV致瘤的主要机制, NKTCL肿瘤细胞主要表现为EBV潜伏感染Ⅱ型, 以EB病毒核抗原1(Epstein-Barr virus nuclear antigen, EBNA1)、潜伏膜蛋白1/2(latent membrane protein, LMP1/2)等抗原表达为主, 这些异常表达的蛋白在信号转导和免疫应答等方面发挥了重要的调控作用[11]. 多项研究发现, LMP-1可通过丝裂原活化蛋白激酶/细胞外调节蛋白激酶1/2(mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2, MAPK/ERK1/2)、Janus相关激酶/信号转导子和转录激活子(Janus-associated kinase/signal transducer and activator of transcription, JAK/STAT)、核因子κB(nuclear factor, NF-κB)、磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, Akt)/雷帕霉素哺乳动物靶标(mammalian target of rapamycin, mTOR)等多条下游信号通路上调survivin、myc、可溶性IL-2受体α和程序性死亡蛋白配体1(programmed death ligand 1, PD-L1)的表达, 从而减少NKTCL细胞凋亡, 促进细胞增殖和侵袭, 介导免疫逃逸等过程[12~17](图1).

高通量基因组测序的应用进一步揭示了EBV诱导NKTCL发生发展的具体分子机制. 有研究发现, NKTCL样本中存在EBV基因组的多克隆现象和EBV基因片段整合插入事件, 从而导致相关区域基因的异常表达, 比如BART区域miRNA的表达缺失和NHEJ1的异常低表达. 此外, 该研究还发现NKTCL存在特异的EBV基因组序列突变特征, 其编码基因的表达谱与其他EBV相关肿瘤(如鼻咽癌、胃癌等)存在显著差异, 说明EBV可能通过独特的分子机制参与NKTCL的致病过程, 提示存在具有特定转化能力的疾病特异性EBV亚型[18]. 另一项基于基因组测序、拷贝数变异分析和转录组测序的多组学研究鉴定出三种NKTCL分子亚型[19]. 其中, MB亚型LMP1表达水平较低(类似潜伏感染Ⅰ型), HEA亚型表现为潜伏感染Ⅱ型并具有较高水平的裂解基因*BNRF1*表达, TSIM亚型也表现为潜伏感染Ⅱ型但高表达另一裂解基因*BALF3*, 这三种分子亚型具有不同的EBV潜伏感染类型及病毒基因表达特征, 并与不同的临床结局相关. Xiong等人[20]利用多组学方法将NKTCL分为不同免疫表型并探索了EBV基因表达模式与免疫微环境特征的联系, 发现EBV可通过调控G蛋白偶联受体(G protein-coupled receptors, GPCR)信号通路, 上调CCR1表达水平, 从而介导免疫抑制, 是潜在的治疗靶点.

一项采用全基因组变异信息和关联分析方法的遗传学研究确定了3个NKTCL易感基因位点, 即*HLA-*

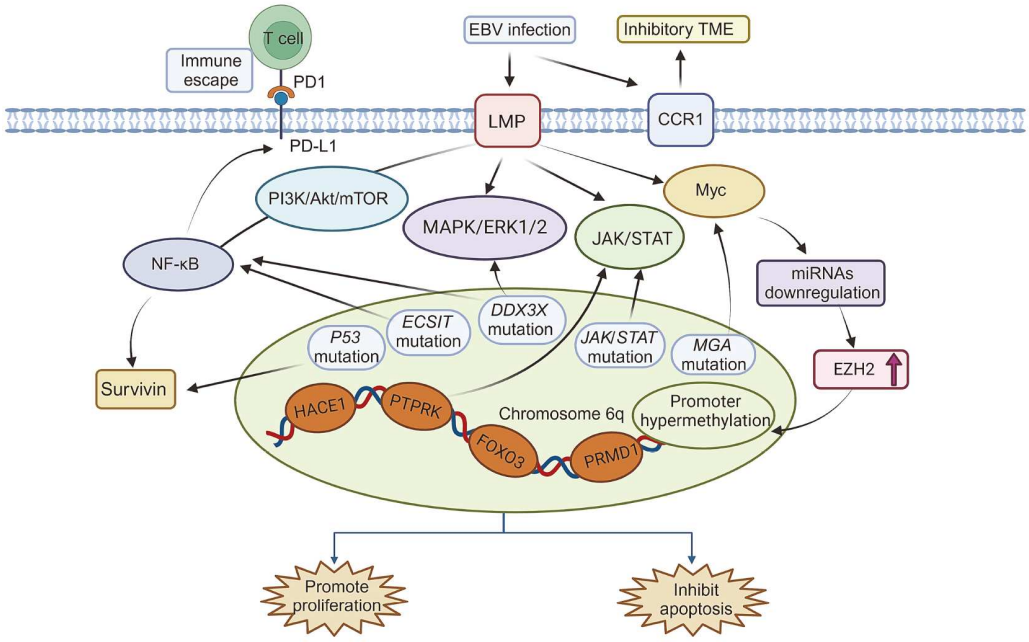

图 1　NKTCL的分子致病机制
Figure 1　Molecular pathogenesis of NKTCL

DPB1(rs9277378), *IL18RAP*(rs13015714)和*HLA-DRB1*(rs9271588). 研究发现, *HLA-DRB1*与EBV感染最为密切, 携带*HLA-DRB1*风险等位基因个体的抗原呈递能力较差, 无法有效清除EBV感染细胞, 最终导致NKTCL的发生和发展[21,22]. RASGRPI是T细胞增殖和抗EBV免疫反应的T细胞特异性核苷酸交换因子, *RASGRPI*的缺失突变也可能导致对EBV感染及EBV相关淋巴增殖性疾病的高易感性[23]. 上述研究表明, NKTCL的分子致病过程受EBV和多个基因的共同调控, 与机体抗病毒免疫应答的遗传学差异相关.

1.2　染色体异常

多项基因组学研究通过比较基因组杂交技术(comparative genomic hybridization, CGH)分析发现, 超过50%的NKTCL患者存在6q21-q25区域等位基因缺失, 这一缺失导致多个肿瘤抑制基因(如*PRDM1*, *FOXO3*, *PTPRK*和*HACE1*等)失活[24~26]. 此外, 在NKTCL患者的其他染色体上亦可观察到拷贝数变异(copy number variations, CNVs)现象, 其中包括染色体1p, 17p和12q的缺失, 以及染色体2q, 13q和10q的扩增[27]. 上述遗传学事件的发生与NK/T细胞发生恶性转化、细胞周期加速、JAK-STAT和NF-κB信号通路异常激活相关[28]. 此外, Xiong等人[19]在识别NKTCL分子亚型的多组学研究中发现, TSIM亚型特征包括6号染色体长臂缺失和9号染色体短臂PD-L1/2基因区段扩增, 伴随下游JAK-STAT信号通路、免疫相关NK细胞介导细胞毒性及抗原呈递通路的激活; MB亚型则表现为1号染色体短臂(1p22.1)*BRDT*基因区段的杂合性缺失, 并激活MAPK, WNT和NOTCH信号通路.

1.3　基因突变

全外显子测序和靶向测序揭示了NKTCL中常见的体细胞突变基因包括RNA解旋酶基因*DDX3X*、抑癌基因*TP53*和*MGA*, 以及JAK-STAT信号通路中的*JAK3*, *STAT3*和*STAT5B*等[29]. *DDX3X*突变导致RNA解旋酶活性受抑, 表现为对细胞周期进程的抑制效应减弱, 以及NF-κB和MAPK信号通路的转录激活, 是患者预后不良的分子标志[29]. *TP53*对凋亡抑制蛋白survivin起负调控作用, *TP53*突变失活导致survivin表达上调, 使得肿瘤细胞凋亡减少[30]; *MGA*是MYC信号通路的负调控因子, 可抑制MYC依赖性的细胞生长和恶性转化[31], 其在NKTCL致病过程中的具体机制仍有待进一步阐明.

JAK3, *STAT3*和*STAT5B*等基因突变造成JAK/STAT

通路的异常激活是肿瘤细胞持续增殖的原因之一，并且已被证实是NKTCL发病的关键因素[32]. Koo等人[33]对65例NKTCL患者样本进行高通量测序，在35.4%的病例中检测到*JAK3*突变，*STAT3*突变则相对少见(约20%). 有研究发现，部分*STAT3*位点的突变(p.D427H, E616G, p.E616K和p.E696K)可增加STAT3的磷酸化水平和转录活性, 并诱导NKTCL肿瘤细胞表达PD-L1, 促进免疫逃逸[15]. *PTPRK*片段缺失和*PTPRK*启动子的异常高甲基化通过磷酸化STAT3从而引起JAK/STAT通路的持续激活，从而促进NKTCL肿瘤增殖和进展[34]. 此外，另一项研究报道，在NKTCL中*ECSIT*基因V140A的突变，可导致NADPH氧化酶活性增强和NF-κB信号通路的异常激活, 容易诱发噬血细胞综合征[35].

1.4 表观遗传调控异常

表观遗传学调控异常是NKTCL的另一个重要特征，研究发现多个表观遗传修饰基因(*EZH2*，*MLL2*，*ARID1A*，*NKT2D*，*TET2*，*BCOR*和*ASXL3*)[36]在NKTCL患者中异常表达. EZH2是一种组蛋白甲基转移酶，通过催化组蛋白H3赖氨酸27(H3K27)的甲基化抑制抑癌基因在转录水平上的表达，从而影响细胞的正常生理功能. 有研究指出，NKTCL肿瘤细胞*EZH2*的mRNA和蛋白质表达均显著升高[37]，这一过程可能与MYC通路激活相关，该激活过程可通过抑制负调控*EZH2*的微小RNA(microRNA)实现[38]. *BCOR*(BCL6共抑制物)是PRC1复合物的成员，能够与特定的组蛋白去乙酰化酶家族基因相互作用[39]. 在NKTCL中，*BCOR*的突变率介于12%~32%之间[40,41]，这些突变可能导致*BCOR*功能失活，然而BCOR在NKTCL致病过程中的具体机制仍有待进一步阐明. 此外, 有研究报道, miR-101, miR26b, miR26a, miR-28-5和miR-363等miRNAs在NKTCL中显著下调，介导了TP53和MAPK等致癌信号通路的异常激活[42], 从而促进肿瘤发生发展.

2 诊断与鉴别诊断

NKTCL的诊断方法包括组织病理学、免疫组化和基因检测等. NKTCL的典型组织学特征表现为肿瘤细胞浸润和坏死，免疫组化常用标志物，如CD3ε, CD56及EBER原位杂交等来确认诊断. 虽然大部分NKTCL病例无TCR基因重排，但特定基因的突变，如*DDX3X*和*ECSIT*，可以作为预后指标. 此外，EBV感染是诊断的重要参考，需通过EBER原位杂交验证. 整体上，NKTCL的诊断需综合考虑多种病理特征和分子标志物.

2.1 组织病理学

NKTCL的组织学特征与受累部位无直接关联. NKTCL的典型病理学特征为常可见凝固性坏死及血管壁纤维素样变性, 异型淋巴样细胞弥漫浸润, 部分病例可见血管中心性生长模式或血管破坏，肿瘤多由中等大小的肿瘤细胞混杂小细胞和(或)大细胞构成，细胞核不规则, 染色质深, 核仁不明显或较小, 胞浆淡染或透明, 核分裂及凋亡易见, 常伴有较显著的炎症细胞浸润[43]. 部分病例可出现鳞状上皮假上皮瘤样增生, 可被误诊为高分化鳞状细胞癌.

2.2 免疫组化

NKTCL诊断所需免疫组化标志物包括胞浆CD3ε, CD2, CD5, CD56, CD4, CD8, CD20, PAX5, 细胞毒标记(TIA-1, Granzyme B, Perferin), Ki-67及EBER原位杂交等. NKTCL典型的免疫表型为胞浆CD3ε(+)，CD56(+), CD5(−), 细胞毒标记(+)和EBER原位杂交(+)[44~46]. 值得一提的是，约20%的病例呈CD56(−). CD43和CD45RO多呈阳性表达, CD7呈不同程度的表达. 其他T细胞和NK细胞相关抗原(如CD4，CD8，CD16和CD57)通常为阴性，而细胞毒T细胞来源的病例则可表达CD5，CD8和T细胞受体(TCRγδ或TCRαβ)[47,48]. 约50%的患者不同程度表达CD30. EBV感染是诊断NKTCL的关键因素，EBV-DNA阳性并非是NKTCL的诊断指标，需通过EBER原位杂交确认[49,50]，当EBV-EBER阴性时诊断要谨慎.

2.3 基因检测

60%~90%的NKTCL无TCR基因重排. 部分基因与NKTCL的预后相关: RNA解旋酶DDX3X基因在NKTCL中存在高频突变, 预示着患者预后不良[29]; *ECSIT*基因V140A的突变，使NKTCL患者更易患噬血细胞综合征[35]. 循环肿瘤DNA(circulating tumor DNA, ctDNA)甲基化诊断模型的应用，展现出在精确区分NKTCL与健康人群、鼻咽癌以及鼻咽部炎症方面的潜力[51].

2.4 鉴别诊断

NKTCL的鉴别诊断可通过其常见于结外部位尤其是上呼吸消化道, 表面CD3, CD5, TCR受体缺失, EBV-DNA水平升高等特点来判断. 需要与其他淋巴瘤以及EBV相关血液病相鉴别, 如外周T细胞淋巴瘤(peripheral T cell lymphomas, PTCL)[52]、弥漫大B细胞淋巴瘤[53]、EBV相关噬血细胞性淋巴组织细胞增生症(hemophagocytic lymphohistiocytosis, HLH)[54,55]等.

3 预后模型与生物学标志物

在门冬酰胺酶治疗时代之前, NKTCL风险分层预后模型主要依赖国际预后指数(International Prognostic Index, IPI)、韩国预后指数(Korean Prognostic Index, KPI)和列线图(nomogram)预后模型, 这些模型在接受蒽环类化疗药物的患者中得到了验证[56]. 然而, 随着以门冬酰胺酶为基础的化疗方案成为NKTCL的标准治疗手段, 这些模型在临床实践中显示出一定局限性, 并逐渐被NKTCL预后指数(prognostic index of natural killer lymphoma, PINK)/PINK-E、列线图简化风险指数(nomogram-revised risk index, NRI)等新型预后评估模型所取代.

Kim等人[57]通过回顾性分析国际38个医疗中心527例NKTCL患者的数据, 识别了4个影响患者OS和无进展生存期(progression-free survival, PFS)的独立预后不良因素, 分别为年龄>60岁、Ann Arbor分期Ⅲ/Ⅳ期、远处淋巴结受累和非鼻腔病变, 并在此基础上构建了PINK预后分层模型. 另外, 该研究还发现, 血浆EBV-DNA阳性同样为NKTCL的独立预后因素, 结合血浆EBV-DNA和PINK模型衍生了PINK-E预后模型, 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. NRI模型综合了美国东部肿瘤协作组(Eastern Cooperative Oncology Group, ECOG)评分、乳酸脱氢酶水平、Ann Arbor分期(Ⅱ期计1分、Ⅲ/Ⅳ期计2分)、原发肿瘤侵犯(primary tumor invasion, PTI)和年龄共五个独立预后不良因素, 将患者分为早期低危、中低危、中高危和高危四个不同风险组. 早期患者中NRI低危、中低危、中高危和高危组的5年OS分别为85.4%, 78.7%, 69.5%和56.3%; 与Ann Arbor分期, IPI, KPI, PINK相比, NRI在验证队列中对OS的预测准确性更高. 决策曲线分析显示, NRI在较大阈值概率范围内提供了最高的净获益[58].

上述NKTCL预后模型主要基于临床预后因素, 尚无反映肿瘤生物学行为的分子指标. 为了弥补这一不足, 有研究采用高通量SNP芯片技术, 成功筛选出与生存相关的36个SNP位点, 并进一步联合临床指标, 构建了一个7联SNP预测模型. SNP分子标签在训练队列和三个验证队列中均显示出良好的预后预测功效, 依据该分类系统区分出的具有高风险和低风险评分的患者具有显著不同的PFS(P<0.001)和OS(P<0.001)[59]. 另一项研究通过液体活检结合高通量全基因组甲基化测序技术, 鉴定出与NKTCL患者预后密切相关的ctDNA甲基化位点, 构建了新型PINK-C预后模型. 使用PINK-C模型在训练队列和验证队列预测的数值和实际观察到的3年OS和3年PFS之间具有良好的一致性, 可协助对NKTCL患者进行预后评估[51]. 相较于单纯临床预后模型, 结合分子标记物的预后模型在指导个体化精准治疗方面更具优势, 但仍需经过大规模临床队列的验证来进一步证实其临床应用价值.

既往研究已经确立了血浆循环游离的EBV-DNA作为EBV相关肿瘤, 包括NKTCL的生物标志物地位[60]. 多项研究提示, NKTCL患者的治疗反应和临床预后与血浆EBV-DNA水平密切相关[61,62]; 此外, 治疗后的EBV-DNA还被用作监测肿瘤微小残留病变(minimal residual disease, MRD)的分子标志物, 这对于评估治疗效果和预测复发风险具有重要临床意义[63]. ctDNA作为肿瘤细胞的遗传物质片段, 其水平和变化能够反映肿瘤的负荷和动态改变[64]; 前文提及的研究进一步指出, ctDNA的甲基化状态也可以作为NKTCL疾病动态监测的分子标志物, 能够提供关于疾病进展、治疗响应和预后的额外信息[51].

4 治疗

4.1 治疗原则

早期NKTCL患者和晚期患者的治疗原则不同, 早期以放疗和化疗综合治疗为主, 而晚期以单纯化疗为主. 早期NKTCL的治疗建议进行风险分层的治疗.

4.2 早期NKTCL的治疗

4.2.1 治疗模式的选择

早期NKTCL的治疗主要采用放疗和化疗综合治疗(combined modality therapy, CMT). 对于Ⅰ/Ⅱ期的NKTCL患者, 推荐进行受累野放疗(involved site radiotherapy, IFRT)[65], 同时, 基于门冬酰胺酶或培门冬酶的化疗方案已被广泛证实为初治NKTCL患者的首选治疗方法, 其能有效控制肿瘤进展, 显著延长患者生存[66~68].

NKTCL常用的综合治疗策略包括序贯治疗、同步放化疗和夹心放化疗三种治疗模式. 尽管三种治疗模式疗效相当, 但目前序贯治疗是最为常用的治疗模式. 对初治NKTCL患者首先采用化疗, 可使得肿瘤体积迅速缩小, 进而提高放疗的准确性和效果, 同时患者在接受放疗时的耐受性更好, 这使得序贯治疗在多数医疗中心得以广泛应用. 尽管同步放化疗在理论上具有潜在的疗效优势, 但由于其实施的复杂性以及可能引发的严重黏膜和全身毒性, 特别是在老年患者中, 其耐受性较差. 因此, 这种方法在某些情况下可能被考虑, 但它并不是所有患者的首选.

值得注意的是, 目前尚缺乏足够证据支持的大规模前瞻性随机临床试验来对比这些不同放化疗组合的疗效. 因此, 关于最佳的综合治疗模式仍存在争议. 各医疗中心通常根据自身经验和患者具体情况制定个性化的治疗方案. 未来, 需要更多的临床研究来明确不同治疗策略的效果, 从而为NKTCL患者提供更为精准和有效的治疗选择.

4.2.2 放疗

超过70%的NKTCL患者在首次诊断时处于疾病早期阶段, 放射治疗在这一阶段的治疗中占据核心地位[56,69~72]. 放射治疗的照射野和剂量选择对于早期NKTCL的治疗效果至关重要, 与肿瘤局部控制率和预后密切相关. 对于早期UAT-NKTCL患者, 推荐采用受累野照射, 并给予50 Gy以上的根治性剂量(可单独应用或联合化疗)[73], 低于50 Gy的放射治疗剂量易导致局部肿瘤复发[58,74,75]. 近年来, 调强放疗(intensity modulated radiation therapy, IMRT)技术的运用, 不仅减少了对周围正常组织的辐射损伤, 同时确保了肿瘤靶区的充分覆盖[76], 能够显著改善患者的生存结果(OS和PFS), 同时毒性可控[77,78]. 一项针对Ⅰ/Ⅱ期鼻部NKTCL患者的回顾性研究发现, 与三维适形放射治疗相比, 无论是否联合化疗, IMRT均能获得更优的5年PFS(68.9% *vs*. 58.2%)和OS(75.9% *vs*. 67.6%)[78]. 然而, 单纯放疗的早期NKTCL与高复发率相关[3], 因此, 推荐早期NKTCL患者进行风险分层的治疗策略: 对于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)的患者, 单纯放疗与综合治疗结果相似. 单纯放疗、放疗后化疗和化疗后放疗的5年OS分别为88.8%, 86.9%和86.3%(*P*=0.972). 对于Ⅰ期伴有危险因素及Ⅱ期患者, 放疗与化疗的综合治疗是标准治疗方案[65].

在确定放疗照射野时, 推荐使用ISRT策略, 该策略将放射治疗照射的区域精确地限定在受累的部位[76]. 当单纯放疗作为主要治疗手段时, ISRT的剂量建议为50~55 Gy; 若放疗与化疗联合应用, 则剂量建议为45~56 Gy. 在单独使用ISRT时, 临床靶区(clinical target volume, CTV)应包括通过对比增强MRI和对比增强CT扫描所确定的受累区域, 并适当扩大范围以涵盖任何初诊时受累的完整解剖结构及相邻的高危区域. 在软组织中, 应额外扩大0.5~1 cm的范围以确保充分覆盖.

4.2.3 同步放化疗

基于同步化疗能够增强肿瘤细胞对放疗敏感性的理论[7], 同步放化疗(concurrent chemoradiotherapy, CCRT)结合或不结合序贯化疗被推荐作为早期NKTCL的有效治疗选择. 目前, 已有临床证据表明, VIPD(依托泊苷、异环磷酰胺、顺铂和地塞米松)、DeVIC(地塞米松、依托泊苷、异环磷酰胺和卡铂)和VIDL(依托泊苷、异环磷酰胺、地塞米松和左旋门冬酰胺酶)化疗方案可与放疗同步进行, 在Ⅰ/Ⅱ期NKTCL中可取得不错的疗效(表1)[79~95].

日本临床肿瘤学组开展的一项I/II期研究(JCOG0211研究)纳入了33名Ⅰ/Ⅱ期UAT-NKTCL高危患者(淋巴结受累, B症状和LDH升高)给予同步放化疗(DeVIC)序贯3个疗程的DeVIC化疗[96]. 中位随访32个月, 2年OS为78%, CRR为77%. 长期随访(中位随访时间为68个月)数据显示, 5年PFS和OS分别为67%和73%[97]. 安全性方面, 晚期毒性可控, 仅少数患者出现3~4级不良事件. 最近的一项回顾性研究(纳入358名患

表 1 放化疗治疗早期、晚期NKTCL的部分临床试验结果[a)]

Table 1 Summary of selected clinical trial results on chemoradiotherapy for early-stage and advanced NKTCL[a)]

分期	类型	研究方法	患者数量	治疗方案	中位随访(月)	ORR(%)	CR(%)	OS(%)	PFS(%)	参考文献
Ⅰ/Ⅱ	CT + RT + CT	前瞻性	26	RT与LVP	27	89	81	89 (2y)	81 (2y)	[105]
Ⅰ/Ⅱ	CT + RT + CT	前瞻性	26	RT 与 LVP	67	89	81	64 (5y)	64 (5y)	[67]
Ⅰ/Ⅱ	CT + RT + CT	前瞻性	40	RT与MESA	25	92	89	92 (2y)	89 (2y)	[110]
Ⅰ/Ⅱ	CT + RT + CT	回顾性	38	RT与P-GEMOX	16	92	87	87 (1y)	87 (1y)	[68]
Ⅰ/Ⅱ	CT + RT + CT	回顾性	35	RT与P-GEMOX	36	94	80	83 (2y)	77 (2y)	[107]
Ⅰ/Ⅱ	CT + RT + CT	前瞻性	36 33	RT与SVILE RT与P-GEMOX	30 29	92 97	83 97	89 (3y) 97 (3y)	88 (3y) 93 (3y)	[79]
Ⅰ/Ⅱ	CT + RT + CT	前瞻性	26	RT与GDP-ML	26	85	77	92 (1y) 88 (2y)	84 (1y) 80 (2y)	[80]
Ⅰ/Ⅱ	CT + RT + CT	前瞻性	52	RT与GELAD	32	94	92	94 (4y)	90 (4y)	[111]
Ⅰ/Ⅱ	CT + RT + CT	前瞻性	58	RT与PEG-Asp + sintilimab + anlotinib	23	88	88	98 (2y)	88 (2y)	[81]
Ⅰ/Ⅱ	CT + RT	前瞻性	27	RT + GELOX	27	96	74	86 (2y)	86 (2y)	[66]
Ⅰ/Ⅱ	CT + RT	回顾性	26	改良SMILE + RT	32	NA	65	87 (2y)	56 (2y)	[112]
Ⅰ/Ⅱ	CT + RT	回顾性	78	RT + DICE-L-asp	60	100	91	89 (5y)	82 (5y)	[109]
Ⅰ/Ⅱ	CT + RT	回顾性	202	RT + P-GEMOX	44	96	83	85 (3y)	75 (3y)	[108]
Ⅰ/Ⅱ	CT + RT	前瞻性	30	RT + DDGP	35	83	73	86 (5y)	83 (5y)	[113]
Ⅰ/Ⅱ	RT + CT	回顾性	44	RT + GDP	38	95	89	85 (3y)	77 (3y)	[82]
Ⅰ/Ⅱ	RT + CT	前瞻性	37 37	RT + GDP + chidamide RT + GDP	43 43	87 78	NA NA	89 (2y) 84 (2y)	75 (2y) 70 (2y)	[83]
Ⅰ/Ⅱ	CCRT	前瞻性	27	RT + DeVIC	32	81	77	78 (2y) 73 (5y)	NA 67 (5y)	[96,97]
Ⅰ/Ⅱ	CCRT	回顾性	150	RT + DeVIC	67	89	82	72 (5y)	61 (5y)	[98]
Ⅰ/Ⅱ	CCRT	回顾性	12	RT与MPVIC-P	81	100	100	100 (5y)	100 (5y)	[84]
Ⅰ/Ⅱ	CCRT + CT	前瞻性	30	CCRT与VIPD	NA	83	80	86 (3y)	85 (3y)	[101]
Ⅰ/Ⅱ	CCRT + CT	前瞻性	62	CCRT与VIDL	49	NA	97	83 (3y) 80 (5y)	77 (3y) 70 (5y)	[99]
Ⅰ/Ⅱ	CCRT + CT	前瞻性	30	CCRT与VIDL	44	NA	87	73 (5y)	60 (5y)	[85]
Ⅰ/Ⅱ	CCRT + CT	前瞻性	28	CCRT与GDP	38	91	84	88 (3y)	84 (3y)	[86]
Ⅰ/Ⅱ	CCRT + CT	回顾性	13	CCRT与ESHAP	38	100	92	72 (2y)	90 (2y)	[87]
Ⅰ/Ⅱ	CCRT + CT	前瞻性	66	CCRT与LVDP	24	86	83	70 (3y)	67 (3y)	[88]
Ⅰ/Ⅱ	CCRT + CT	前瞻性	30	CCRT与PEG-Asp	27	100	100	91 (2y)	93 (2y)	[89]
Ⅰ/Ⅱ	CCRT + CT	前瞻性	30	CCRT与P-GDP	52	93	93	93 (5y)	89 (5y)	[90]
Ⅲ/Ⅳ	Mainly CT	前瞻性	20	SMILE	24	80	40	45 (1y)	45 (1y)	[104]
Newly diagnosed	Mainly CT	前瞻性	43	SMILE	31	84	65	47 (5y)	60 (4y)	[91]
Ⅲ/Ⅳ	Mainly CT	回顾性	17	改良SMILE	32	NA	43	21 (2y)	18 (2y)	[112]
Newly diagnosed	Mainly CT	回顾性	96	P-GEMOX	17	91	60	76 (3y)	65 (3y)	[92]
Ⅲ/Ⅳ	Mainly CT	前瞻性	42	DDGP	14	95	71	90 (1y) 74 (2y)	86 (1y)	[93]
Ⅲ/Ⅳ	Mainly CT	前瞻性	40 40	SMILE DDGP	42 42	60 90	48 68	52 (5y) 74 (5y)	42 (3y) 57 (3y)	[94]
Ⅲ/Ⅳ	CT	前瞻性	64	DDGP	40	80	61	82 (1y) 75 (2y) 75 (3y)	77 (1y) 68 (2y) 62 (3y)	[95]

a) NA, not available, 无数据; y, year, 年; GDP-ML: gemcitabine, cisplatin, dexamethasone, methotrexate, pegaspargase, 吉西他滨、顺铂、地塞米松、甲氨蝶呤、培门冬酶; GDP: gemcitabine, cisplatin, dexamethasone, 吉西他滨、顺铂、地塞米松; MPVIC-P: ifosfamide, carboplatin, methotrexate, peplomycin, etoposide, 异环磷酰胺、卡铂、甲氨蝶呤、培洛霉素、依托泊苷; ESHAP: etoposide, cisplatin, cytarabine, methylprednisolone, 依托泊苷、顺铂、阿糖胞苷、甲泼尼龙; LVDP: L-asparaginase, cisplatin, etoposide and dexamethasone, 左旋门冬酰胺酶、顺铂、依托泊苷、地塞米松; P-GDP: pegaspargase, gemcitabine, dexamethasone, cisplatin, 培门冬酶、吉西他滨、地塞米松、顺铂

者; 257名患者为早期NKTCL)也报道了使用DeVIC方案同步放化疗治疗NKTCL的结果[98]: 中位随访6年后, 5年OS和PFS分别为72%和61%. 然而在该研究中, 仅有4%的早期NKTCL患者根据PINK模型被归类为高风险.

在早期鼻型NKTCL患者中使用同步放化疗后序贯化疗的安全性和有效性也已在最近的研究中得到证实[99,100], 例如, VIDL化疗联合放疗的同步放化疗方案的ORR和CR分别为90%和87%, 5年PFS和OS分别为60%和73%[99]. 一项Ⅱ期研究报道了采用同步放化疗(顺铂联合放疗)序贯3个周期VIPD化疗在30名NKTCL患者(21名患者为Ⅰ/Ⅱ期疾病, 9名患者为Ⅲ/Ⅳ期疾病)中的结果: 同步放化疗后CRR为73%, 序贯VIPD化疗后ORR和CRR分别为83.3%和80%, 估计的3年PFS和OS分别为85%和86%[101].

然而, 研究也发现, 患者可能出现与CCRT相关的长期不良事件, 尤其是口腔炎和鼻黏膜炎, 这些不良事件对患者的生活质量产生影响[102]. 因此, 在制定治疗策略时, 需进行个体化的风险评估, 以确保为患者提供最佳的综合治疗方案.

4.2.4 序贯治疗

传统的基于蒽环类药物的CHOP方案并序贯放疗虽然有一定疗效, 但5年PFS和OS仅为54%和65%, 结果并不理想[103]. 相比之下, 使用含门冬酰胺酶的治疗方案序贯放疗在NKTCL中观察到更高的ORR(90%~100%)和CR率(74%~91%). 此类化疗方案包括P-GEMOX(培门冬酶、吉西他滨和奥沙利铂)[104,105]、LVP(左旋门冬酰胺酶、长春新碱、泼尼松龙)[67,106]、SMILE(地塞米松、甲氨蝶呤、异环磷酰胺、左旋门冬酰胺酶和依托泊苷)[107]、GELOX(吉西他滨、左旋门冬酰胺酶和奥沙利铂)[66,108]、DICE-L(地塞米松、异环磷酰胺、顺铂、依托泊苷、左旋门冬酰胺酶)[109]、MESA(甲氨蝶啶、依托泊苷、地塞米松和培门冬酶)[110]和GELAD(吉西他滨、依托泊苷、培门冬酶、地塞米松)[111]. 在使用上述化疗方案的研究中, 5年PFS为64%~83%, 显示出更好的长期疗效. 一项针对NKTCL患者的改良SMILE方案疗效评价的回顾性研究表明, 在接受序贯治疗(2个周期的改良SMILE方案, 随后45 Gy ISRT)的11例早期患者中, 估计的2年PFS为83%, 所有患者在研究发表时仍存活, 没有疾病复发证据[112]. P-GEMOX和DDGP序贯放化疗在Ⅰ/Ⅱ期NKTCL患者中也表现出良好的疗效和可接受的毒性[108,113]. 一项包含303例Ⅰ/Ⅱ期鼻型NKTCL患者的一项大型多中心回顾性研究发现, 使用P-GEMOX序贯化放疗患者的CR率和ORR分别为83%和96%, 3年PFS和OS分别为75%和85%, 结果与同步放化疗合并或不合并巩固化疗的患者相当, 但序贯化放疗的严重血液学毒性和放射诱导的黏膜炎发生率低于CCRT方案[114]. 这表明, 在有效的化疗前提下, 放疗的时机可能不是决定疗效的关键因素.

4.2.5 夹心放化疗

夹心放化疗是另一种可选择的联合化疗与放疗的治疗策略, 即首先进行2个周期化疗, 随后进行ISRT, 并在放疗完成后再进行2~4个周期化疗. 在一项纳入27名初治Ⅰ/Ⅱ期UAT-NKTCL患者的Ⅱ期研究中, 采用GELOX方案进行夹心放化疗, ORR达96%、CR率为74%. 中位随访63个月后, 5年OS和PFS分别为85%和74%; 同时, 该治疗方案表现出较高的安全性, 没有报告与治疗相关的死亡案例[106]. 此外, P-GEMOX方案在夹心放化疗中的应用也取得了良好效果. 一项纳入38名初治UAT-NKTCL的研究显示, 采用P-GEMOX方案心放化疗的ORR为92%, CR为87%. 在中位随访时间为15.5个月时, 患者的1年PFS和OS均达到87%[68]. 另外, 有研究报道, 使用GELOX方案序贯或夹心放化疗治疗早期UAT-NKTCL患者的结果, 5年OS、PFS和局部区域复发率(locoregional recurrence rate, LRR)分别为85%, 79%和17%. 其中, 夹心放化疗与更高的PFS和改善的LRR相关(P=0.01)[115]. 夹心放化疗作为早期NKTCL的一种治疗策略, 其疗效与序贯放化疗相当, 但伴随着更高的不良反应发生率[116]. 为了更准确地评估其长期获益和安全性, 需要在更大的临床试验中进行深入研究和验证.

4.3 晚期NKTCL的治疗

晚期NKTCL的标准治疗通常以门冬酰胺酶为基础的单纯化疗方案为主. 现有的指南推荐化疗方案包括P-GEMOX, SMILE, DDGP(地塞米松、顺铂、吉西他滨和培门冬酶)和AspaMetDex(L-天冬氨酸酶、甲氨蝶呤和地塞米松). 在既往一项随机对照研究中, DDGP与SMILE治疗初治晚期NKTCL的CR率无显著差异,

但DDGP组ORR显著高于SMILE组，分别为90.0%和60.0%. 此外，DDGP组的3年PFS率和5年OS也均高于SMILE组(3年PFS, 56.6% *vs*. 41.8%; 5年OS, 74.3% *vs*. 51.7%). 在安全性方面, SMILE组的3级和4级血液学毒性发生率(白细胞减少85.0% *vs*. 62.5%; 中性粒细胞减少85.0% *vs*. 65.0%)高于DDGP组; 同时SMILE组非血液学毒性也更为显著. 值得注意的是, SMILE组治疗相关死亡率高达17.5%，而DDGP组死亡发生率仅为2.5%. 另一项对比P-GEMOX方案与AspaMetDex方案治疗初治晚期NKTCL的前瞻性临床研究显示，P-GEMOX和AspaMetDex的ORR分别为87.1%和66.6%. AspaMetDex组发生了3例治疗相关死亡，而P-GEMOX组无治疗相关死亡发生, 提示P-GEMOX方案在临床应用中的安全性更佳.

尽管采用标准化疗方案, 晚期NKTCL患者的长期缓解率仍仅为30%，超过70%的患者面临复发的风险. 出现化疗耐药的患者预后极差，迫切需要新的有效策略以改善患者的生存状况. 既往研究表明，肿瘤细胞上高PD-L1表达是NKTCL患者不良预后的独立危险因素，多个小样本量研究的结果显示，PD-1单抗在复发/难治NKTCL中表现出潜在的抗肿瘤活性：单药的ORR可达57%~100%. 因此，我们提出了PD-1单抗联合P-GEMOX方案治疗初治晚期NKTCL的免疫化疗新模式, 初步报道的ORR为88.9%, CR率达到77.8%. 不良事件仍以血液学毒性为主，未观察到不可控的不良反应. 为了进一步验证这一策略的有效性和安全性，我们发起了一项前瞻性Ⅱ期临床试验. 结果表明，在入组的34例初治晚期NKTCL患者中，采用信迪利单抗(一种PD-1单抗)联合P-GEMOX方案治疗，ORR高达100%, CR率为85%. 此外, 2年PFS, DFS和3年OS分别为64%，72%和76%. 最常见的3级或4级治疗相关不良事件为中性粒细胞减少症(50%)、贫血(29%)和高甘油三酯血症(29%). 甲状腺功能减退是最常见的免疫相关不良事件(53%), 包括一名患者(1/34例, 3%)的3级甲状腺功能减退, 导致治疗终止. 这些结果表明, 信迪利单抗联合P-GEMOX的免疫化疗新方案在治疗晚期NKTCL中具有良好的耐受性和安全性[117]，值得进一步的临床应用和推广.

造血干细胞移植(hematopoietic stem cell transplantation, HSCT)治疗NKTCL的经验仍然有限，多数研究以回顾性分析为主，缺乏大规模的前瞻性随机对照试验. 早年几项小型研究表明，自体造血干细胞移植(autologous hematopoietic stem cell transplantation, ASCT)对晚期或复发性疾病的益处有限[118~120]. 在采用MEDA方案联合ASCT治疗晚期及难治复发NKTCL的前瞻多中心研究中[121]，中位随访时间48.8个月，全组患者4年OS为58.0%, 4年PFS为43.4%, 接受ASCT的患者的4年PFS为80.0%，4年OS为92.0%；获得CR后未接受ASCT的患者为40.0%, 4年OS为60.0%. 近期, 韩国一项采用VIDL方案诱导后ASCT巩固治疗初诊晚期NKTCL的2期研究显示，17例患者在诱导化疗后接受了ASCT，ASCT后中位PFS为13.2个月，仅47%的患者仍保持缓解[122]. 尽管目前缺少相关的随机对照研究, 但诱导治疗后接受ASCT与仅接受含培门冬酶方案治疗的患者间并无明显生存差异，尚无直接证据证明ASCT可改善晚期NKTCL患者的预后[123]. 另外，针对同种异体造血干细胞移植(allogeneic stem cell transplantation，Allo-SCT)的作用，两项回顾性研究分别对82名北美患者[124]和18例亚洲患者[125]接受Allo-SCT的疗效进行了分析, 北美患者3年OS仅为34%，亚洲患者的5年OS为57%. 移植相关死亡率分别约为30%和22%, 高移植相关死亡率仍然是影响Allo-SCT在晚期和复发/难治性NKTCL患者中应用主要障碍. 近期，一项回顾性分析报道了欧洲和亚洲69家移植中心的135例[126]接受Allo-SCT的患者结果. 中位随访4.8年，1年和3年的复发率分别为29.6%和34.1%，非复发死亡率分别为14.8%和17.3%，PFS分别为55.6%和48.6%，OS分别为66.9%和55.6%; OS显示超过3年后呈平台期. 欧洲SFGM-TC研究[127]评估65名NKTL患者接受HSCT(19例Allo, 46例ASCT)的结果, 中位随访79.9月, ASCT和Allo的4年PFS相似(PFS: 34% *vs*. 26%, P=0.12). 总体而言，尽管HSCT在NKTCL中的治疗经验有限且存在争议，但现有数据表明，对于诱导化疗后达到CR的晚期或复发/难治NKTCL患者，HSCT可能是一种值得考虑的治疗选择. 然而，考虑到其潜在的风险和不确定性, 需要在未来的研究中进一步验证其疗效和安全性.

4.4 新药靶向治疗

尽管基于门冬酰胺酶的治疗方案较蒽环类方案改善NKTCL患者的生存，但复发/难治性(relapsed or refractory，r/r)患者的生存结局仍旧很差，非蒽环类药物一线治疗后复发的中位总生存期仅6个月, 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NKTCL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EB病毒的细胞毒性T淋巴细胞、信号通路抑制剂和纳米小分子药物等(表2, 图2)[128~132].

4.4.1 靶向肿瘤细胞表面抗原的抗体

已有多种细胞表面抗原分子(包括CD38, CD30, CD52, CD25等)被发现在NKTCL肿瘤细胞中表达异常[133~136], 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NKTCL的发生发展中发挥着重要作用. 针对这些靶点, 目前已有多种靶向治疗手

表 2 靶向治疗NKTCL的部分临床试验结果

Table 2 Summary of selected clinical trial results on targeted therapy for NKTCL

	治疗药物		靶点	试验ID	患者数量(可评价/估计)	分期	联用药物	适应人群	NKTCL疗效	参考文献
细胞表面靶向抗体	细胞表面分子靶向抗体	达拉木单抗	CD38	NCT02927925	32	2	–	r/r NKTCL	ORR: 25% CR: 0% 4m PFS: 13% 6m OS: 42.9%	[142]
		维布妥昔单抗	CD30	NCT02280785	33 (7 NKTCL)	2	–	r/r 表达CD30的NHL	ORR:29%	[139]
	EBV靶向CTL	Baltaleucel-T	EBV抗原	NCT01948180	15	2	–	进展期NKTCL	挽救队列: ORR: 50% CR: 30%	[155]
免疫检查点抑制剂	阿维单抗		PD-L1	NCT03439501	21	2	–	r/r NKTCL	ORR: 38% CR:24%	[150]
	舒格利单抗(CS1001)		PD-L1	NCT03595657	80	2	–	r/r NKTCL	ORR:46.2%, CR: 30.4% 1y OS:68.6% 2y OS:54.6%	[149]
	信迪利单抗		PD-1	NCT03228836	28	2	–	r/r NKTCL	ORR: 75.0% 1y OS: 82.1% 2y OS: 78.6%	[147]
	信迪利单抗		PD-1	NCT04127227	63	2	P-GEMOX	初治晚期NKTCL	ORR: 100% CR: 87.5% 1y OS: 100% 1y PFS: 95%	[128]
	信迪利单抗		PD-1	NCT03936452	55	2	培门冬酶、安罗替尼	未治疗的局限期NKTCL	ORR: 87.8% CR: 87.8% 2y PFS: 87.6% 2y OS: 97.9%	[81]
	替雷利珠单抗		PD-1	NCT04038411	50	2	西达本胺、来那度胺、依托泊苷	r/r NKTCL	CR: 50.0% 1y PFS: 86.8%	[129]
	替雷利珠单抗		PD-1	NCT03493451	77 (22 NKTCL)	2	–	r/r成熟T和NK细胞肿瘤	ORR 31.8% CR 18.2%	[130]
表观遗传靶向制剂	西达本胺		HDACi	NCT03820596	37	1/2	信迪利单抗	r/r NKTCL	CR: 59.5% PR: 48.6% 1.5y PFS: 52.5% 1.5y OS: 76.2%	[131]
	西达本胺		HDACi	NCT02878278	24	2	–	r/r NKTCL	CR: 33%	[173]
信号通路抑制剂	硼替佐米		NF-κB	NCT02808091	7	2	GIFOX	初治NKTCL	ORR: 43%	[163]
	塞利尼索(ATG010)		XPO1	NCT04425070	97 (10 NKTCL)	1/2	GEMOX或ICE或替雷利珠单抗	外周T和NK细胞淋巴瘤	ORR: 60% CR: 20%	[132]

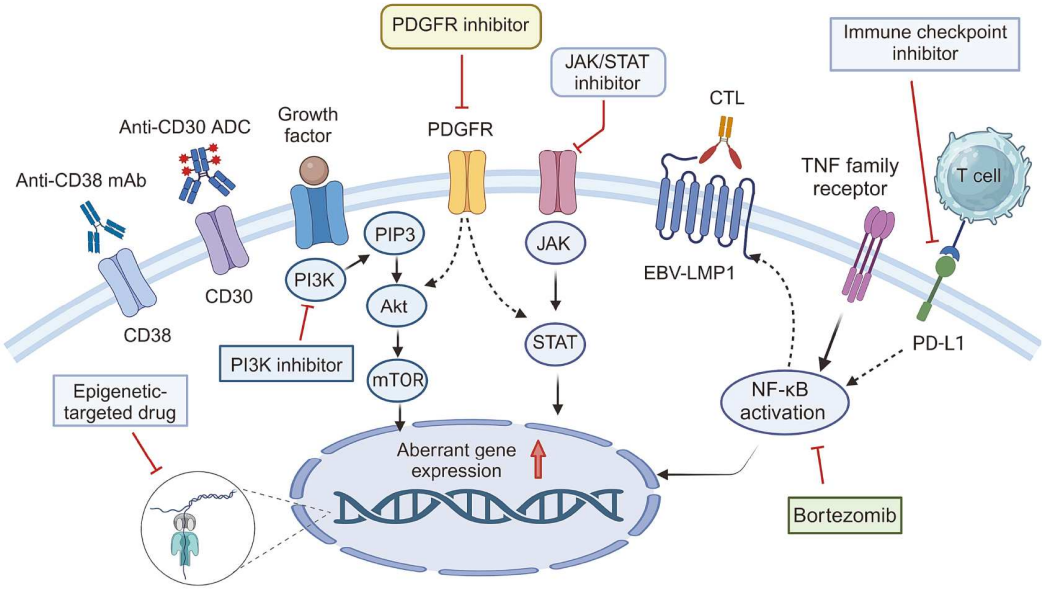

图 2　NKTCL的靶向治疗策略 NKTCL
Figure 2　Targeted therapeutic strategies for NKTCL

段如单克隆抗体(monoclonal antibody, mAb)和抗体偶联药物(antibody-drug conjugate, ADC)等正在NKTCL中开展相关研究.

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. 40%~75%的NKTCL患者肿瘤细胞表达CD30[137,138]. 维布妥昔单抗(Brentuximab vedotin, BV)是一种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[139]. 在一项探索BV单药治疗复发难治性NHL患者(含7例NKTCL)的2期单臂临床试验中, 分别有1例患者达到完全缓解(complete remission, CR)和部分缓解(partial remission, PR)[139].

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传导过程, 有研究显示NKTCL患者的肿瘤细胞高表达CD38[140]. 抗CD38单抗可以通过多种免疫相关机制诱导肿瘤细胞凋亡, 包括补体依赖的细胞毒作用、抗体依赖性细胞介导的细胞毒作用和抗体依赖性细胞吞噬作用等[141]. 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NKTCL患者的2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%[142]. 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[143], 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 NKTCL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高表达的患者比低表达的患者有更好的疗效[144].

此外, CD52, CD25, CD40, CCR4, B7H3和CD70也被认为可能是NKTCL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NKTCL的治疗中, 如靶向CD52的mAb阿仑单抗(Alemtuzumab)[145]、靶向CD25的mAb巴利昔单抗(Basiliximab)[16]等, 相关临床试验正在开展, 未来将为NKTCL患者提供更多的治疗选择.

4.4.2　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, 阻断免疫检查点可使肿瘤反应性T细胞克服调控机制, 并产生有效的抗肿瘤反应[146]. 目前已有多种免疫检查点抑制剂在NKTCL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NKTCL患者的2期单臂临床试验[147], 结果

显示, 28名患者ORR为75%, 2年OS可达78.6%. 另一项使用替雷利珠单抗单药治疗r/r NKTCL患者的2期研究结果显示, 在纳入的22例NKTCL患者中, ORR和CR率仅为31.8%和18.2%, 可能由于该研究所纳入的患者基线肿瘤负荷高所致[148]. 抗PD-L1单抗舒格利单抗治疗80名复发/难治性NKTCL患者的单臂2期临床试验显示ORR和CRR分别为46.2%和30.4%, 1年和2年OS分别为68.6%和54.6%[149]. 在Kim等人[150]进行的一项使用阿维单抗单药治疗r/r NKTCL的2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. 另外, 除了前文中提到EBV驱动的LMP1通过核因子κB(NF-κB)信号通路可增加PD-L1的表达, STAT3激活也可以增加PD-L1的表达[15], 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NKTCL或许是未来值得探索的一个方向.

4.4.3 靶向EBV的细胞治疗

EBV阳性的肿瘤细胞广泛表达潜伏期Ⅱ型EBV抗原, 如LMP1, LMP2和EBV核抗原1(EBNA1), 这些分子被认为与NKTCL细胞的存活和增殖相关[151], LMP1可通过NF-κB通路促进NKTCL细胞的存活、增殖、侵袭和迁移[152]. 在一项纳入52名EBV阳性淋巴瘤患者的1期单臂试验中, 靶向LMP2或LMP1/2的细胞毒性T淋巴细胞(cytotoxic T lymphocytes, CTL)可诱导持久的治疗反应且无明显毒性, 该研究包括11名NKTCL患者, 在其中6名处于疾病活动期的患者中, 4人实现完全缓解[153]. 在另一项研究中, 10名NKTCL患者(8名早期和2名晚期)在经过诱导治疗达到完全缓解后接受自体LMP特异性CTL治疗, 其4年OS和PFS分别为100%和90%[154], 尽管研究结果令人鼓舞, 但由于样本量较小且大多数患者为早期NKTCL, 因此仍需要进一步的研究证实靶向EBV细胞治疗的有效性.

Kim等人[155]进行了一项使用自体EBV特异性T细胞(baltaleucel-T)治疗晚期、复发性NKTCL患者的2期研究, 由于研究纳入的54名患者中有39人出现baltaleucel-T细胞扩增失败, 最终仅15名患者接受了baltaleucel-T治疗, 在10名处于疾病活动期的患者中, 该疗法的ORR和CR率分别为50%和30%, 在其余5名基线无可测量病变的患者中, 有2名在随访5个月内始终保持缓解状态. 总体而言, 这些研究表明, 靶向EBV的细胞疗法可在NKTCL患者中诱导持续的治疗反应, 然而, CTL的扩增技术还需进一步优化.

4.4.4 信号通路抑制剂

基因组表达谱分析(genomic expression profiling, GEP)提示NKTCL患者中存在JAK/STAT, NF-κB, PI3K/Akt/mTOR和PDGFR等信号通路的异常激活[156], 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和NF-κB通路的异常激活是肿瘤细胞持续增殖的原因之一[157,158]. 泛JAK抑制剂CP-690550[33], JAK1/3抑制剂托法替尼[159]以及选择性STAT3抑制剂WP1066[160]可抑制多种NKTCL细胞系的增殖并诱导凋亡. 此外, 有研究发现, STAT3突变的患者往往有高表达CD30的特点[161], 这提示JAK/STAT抑制剂与抗CD30抗体联用治疗NKTCL可能更为有效. 目前有两项临床试验正在开展, 以评估JAK抑制剂stattic(NCT03598959)和鲁索替尼(NCT02974647)治疗复发/难治性NKTCL患者的疗效. 硼替佐米是一种间接抑制NF-κB通路的蛋白酶体抑制剂[162], 在一项仅纳入7名NKTCL患者的2期试验中, 硼替佐米与GIFOX(吉西他滨、异环磷酰胺、奥沙利铂)方案联合治疗具有43%的ORR(一名患者CR)[163]. 此外, 有研究表明, Bortezomib能够诱导EBV从潜伏期进入裂解期[164], 这提示可以考虑使用硼替佐米与靶向EBV的CTL进行联合治疗.

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[165]. 一项研究显示, NKTCL患者高表达多种PI3K同工酶(PIK3α, PIK3β, PIK3γ和PIK3δ), 同时PI3Kα高表达与患者不良预后相关[166], 该研究还显示, 库潘尼西(一种针对PI3Kα和PIK3δ的抑制剂)可以减少Akt的磷酸化, 并在体内外抑制肿瘤生长. 在一项探索PI3Kδ抑制剂林普利塞治疗r/r PTCL的2期研究中, 所纳入的8例r/r NKTCL患者治疗后均产生应答[167]. 另一项研究中, mTOR抑制剂(雷帕霉素和CCI-779)将NKTCL细胞阻滞在G1期并减弱了细胞的生存能力[168], 表明mTOR抑制剂也可能是NKTCL治疗的潜在选择. PDGFRα是一种受体酪氨酸激酶, 可与JAK/STAT和PI3K/Akt信号通路中的关键蛋白相互作用[169]. 高水平的PDGFRα已被证实与NKTCL患者的不良预后相关[170], PDGFR酪氨酸激酶抑制剂伊马替尼

可抑制NKTCL细胞的增殖, 同时诱导细胞周期停滞在G0/G1期[171]. 总的来说, PI3K/Akt/mTOR和PDGFR通路是NKTCL治疗的潜在靶点, 但未来仍需要相关临床试验进一步验证.

4.4.5 表观遗传学靶向药物

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[172]. 西达本胺是HDAC1, 2, 3和10的选择性抑制剂[173]. 一项使用西达本胺单药治疗28例r/r NKTCL患者的2期临床研究结果显示, ORR为39%, 中位PFS和中位OS分别为1.5个月和7.7个月[174]. 在一项纳入37例晚期NKTCL患者的非随机研究中, 19例接受西达本胺联合化疗的患者的ORR为40%, 而其余18例接受西达本胺单药治疗患者的ORR为15%[175]. 在一项针对r/r NKTCL患者的1b/2期单臂研究中, 西达本胺联合信迪利单抗的ORR为58.3%, CR为44.4%, 中位随访时间38.3个月, 3年OS为56%, 中位PFS为23.4个月[176]. 值得注意的是, 抑制组蛋白去乙酰化酶可能触发EBV再激活, 使用罗米地辛(另一种HDACi)已被报道可能引起EBV再激活, 因此在使用HDACi治疗时, 需要观察EBV再激活的风险[177]. 全基因启动子甲基化分析显示, 在NKTCL细胞系和患者样本中, 多个抑癌基因(包括*BCL2L11*, *DAPK1*和*TET2*)的启动子存在高度甲基化, 地西他滨治疗可诱导甲基化基因的重新表达[178], 提示去甲基化药物可能具有治疗作用. 一项使用DNA去甲基化药物(地西他滨或氮杂胞苷)联合PD1抑制剂的探索性研究结果显示, 影像学评估的ORR和CR率分别为59.1%和45.4%, 中位随访时间12.1个月, 1年OS为70.4%, 中位PFS为12.8个月[179].

4.4.6 纳米小分子药物

盐酸米托蒽醌脂质体(PLM60)是全球首个上市的米托蒽醌纳米药物, 可通过干扰肿瘤细胞的DNA合成和功能,抑制肿瘤细胞的生长和分裂[180]. 一项评估PLM60单药治疗R/R PTCL和NKTCL的2期临床试验共纳入108例患者, 包括21例疗效可评估的r/r NKTCL患者, 其ORR为52.4%, CR率为28.6%[181], 表明PLM60在r/r NKTCL中具有一定疗效. 另一项探索PLM60联合替雷利珠单抗治疗r/r NKTCL的1b/2期研究初步结果显示: 在1b期入组的6例患者中, 其CR率、ORR和DCR分别为33.3%, 100.0%和100.0%[182], 提示PLM60与其他新药联用的治疗模式值得进一步探索, 该研究目前仍在进行中(NCT05464433), 相关结果有待进一步报道.

5 总结与展望

近年来, NKTCL的研究取得了显著进展, 尤其在其发病机制和治疗策略方面. 基因层面的深入研究, 结合高通量测序技术, 揭示了该疾病与EBV感染之间的紧密联系, 为NKTCL的分子靶向治疗提供了重要的线索.

近20年, 相较于传统蒽环类药物, 以门冬酰胺酶为基础的化疗方案已显著改善了NKTCL患者的生存结局, 尤其是早期患者. 尽管如此, 初诊晚期和难治复发NKTCL的治疗仍充满挑战[183]. 免疫治疗, 特别是免疫检查点抑制剂的应用, 为晚期和复发患者带来了新的希望. 信号通路抑制剂和表观遗传靶向药物的证据目前仍然有限, 但在部分患者中显示出独特的疗效. 未来, 联合免疫检查点抑制剂、新型靶向药物和化疗的新策略可能有助于提高NKTCL的治疗效果. 同时, 哪些患者选择移植, 如何选择合适的移植时机, 以及如何有效管理药物毒性, 也是未来需要重点研究的问题. NKTCL作为一种具有高度异质性的疾病, 其致病机制和预后因素复杂多样, 不同患者间存在分子和遗传层面的显著差异, 未来仍需要更深入地探究致病机制、开发新型药物治疗靶点并发展个性化的治疗策略.

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Research progress on EBV-associated NK/T cell lymphoma

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NK/T cell lymphoma (natural killer/T-cell lymphoma, NKTCL) is a rare and highly invasive subtype of non-Hodgkin lymphoma, which is closely associated with Epstein-Barr virus (EBV) infection, with a high incidence rate in Asia and Latin America. In recent years, the application of high-throughput sequencing technology has revealed the biological basis of NKTCL heterogeneity and the molecular pathogenic mechanisms, including the silencing of tumor suppressor gene caused by deletion of chromosome 6q21 allele, abnormal activation of several carcinogenic signal pathways due to EBV infection and somatic gene mutation, and abnormal epigenetic regulation. At present, there is no unified treatment standard for NKTCL. In the early stage, radiotherapy and chemotherapy are the main comprehensive treatment, while chemotherapy alone is the main option for the late stage. The prognosis of advanced and relapsed refractory patients is poor, and it is urgent to explore more effective treatment options. With the accelerated evolution of global new drug development, various new drugs against NKTCL are constantly emerging. This review summarizes the research progress in EBV-associated NK/T cell lymphoma.

NK/T cell lymphoma, **EBV**, **chemotherapy**, **radiotherapy**, **immunotherapy**

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