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·专家论坛·

靶碘联合:进展期分化型甲状腺癌治疗新策略

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[摘要]　进展期分化型甲状腺癌缺乏有效的治疗方案、总体预后较差,是临床亟需解决的难题。多靶点酪氨酸激酶抑制剂已获批应用于放射性碘难治性分化型甲状腺癌的治疗,最近也被推荐用于局部进展期分化型甲状腺癌术前新辅助治疗。虽然放射性碘治疗是进展期分化型甲状腺癌术后的标准治疗方案,但存在一定的局限性和限制。多靶点酪氨酸激酶抑制剂联合放射性碘治疗,有望成为进展期分化型甲状腺癌治疗的新策略。

关键词:进展期分化型甲状腺癌;　多靶点激酶抑制剂;　放射性碘;　碘-131

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Combination of targeted multikinase inhibitor and radioiodine: a new strategy of treatment for advanced differentiated thyroid carcinoma

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[Abstract]　Advanced differentiated thyroid carcinoma (ADTC) lacks effective treatment options, and has a poor prognosis, which is an urgent clinical problem to be resolved. Targeted multikinase inhibitor(MKI) has been approved for the treatment of radioiodine refractory differentiated thyroid carcinoma, and have recently been recommended as a preoperative neoadjuvant therapy agents for locally ADTC. Although radioiodine therapy is the standard postoperative treatment for ADTC, it has certain limitations. MKI combined with radioiodine therapy is expected to become a new strategy of treatment for ADTC.

Key words: Advanced differentiated thyroid carcinoma; Multikinase inhibitor; Radioiodine; ^{131}I

分化型甲状腺癌(differentiated thyroid carcinoma, DTC)包括甲状腺乳头状癌(papillary thyroid carcinoma, PTC)、甲状腺滤泡癌(follicular thyroid carcinoma, FTC)以及甲状腺嗜酸细胞癌(oncocytic thyroid carcinoma, OTC),是近年发病率增长较快的恶性实体肿瘤之一,大多数侵袭性低,预后良好[1]。但5%~15%的病人表现为局部进展期病变,约20%的病人发生局部持续/复发性疾病、约10%的病人出现远处转移[2-4],这些进展期DTC(advanced DTC, ADTC)是目前DTC治疗的难点。即使采取标准的治疗方案,包括手术、放射性碘治疗以及促甲状腺激素(thyroid stimulating hormone, TSH)抑制治疗,预后仍较差。约2/3的远处转移性DTC(distant metastatic DTC, DMDTC)发展为放射性碘难治性DTC(radioiodine refractory DTC, RRDTC)[5-6]。酪氨酸激酶抑制剂(tyrosine kinase inhibitor, TKI)类的分子靶向药物,包括多靶点激酶抑制剂(multikinase inhibitor, MKI)如索拉非尼、仑伐替尼、安罗替尼、多纳非尼等,以及特殊单靶点激酶抑制剂如普拉替尼、拉罗替尼等,均因其良好的客观缓解率(objective response rate, ORR)及无进展生存期(progression free survival, PFS)获益,获批用于常规标准治疗后,疾病仍进展的RRDTC的治疗[7]。

近年来,在ADTC的治疗上,有研究者尝试将TKI的应用时机提前,如对于局部进展期DTC(locally advanced DTC, LADTC)在术前应用TKI,使预期无法切除或难以完全切除的病灶获得完整切除的机会,该新辅助/转化治疗方案的有效性及安全性均得到临床初步验证,并已被相关专家共识推荐[8]。那么对于ADTC的术后治疗,尤其是残留病灶较大、总体肿瘤负荷较重的病例,是否也可将TKI应用提前,而不必等到经^{131}I治疗后证实为

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RRDTC 再启动？TKI 联合 ^{131}I 的“靶碘联合”治疗正逐步成为研究热点。因 MKI 可及性高、适用范围广，与 ^{131}I 的联合治疗适合更多的临床场景。本文重点关注该方向的进展。

1 ADTC 的界定

ADTC 的界定主要基于临床判断[9]。肿瘤的临床特征如局部侵犯（侵犯气管、食管、喉、喉返神经等）、区域转移（多区、多个淋巴结转移，淋巴结外侵犯及癌结节）、远处转移以及复发等，均反映肿瘤生物学行为活跃，预示标准治疗效果不佳以及预后不良[9-10]。2022 年，美国头颈学会内分泌外科分会和国际甲状腺肿瘤学组的共识声明，从结构与外科情况、生化特征、组织学与分子特征以及其他临床判断 4 个方面对 ADTC 作出界定（见表 1）[11]。

表 1 ADTC 的界定

Tab 1 Definition of ADTC

特征分类	特征描述
结构/外科	巨大、侵袭性或不可手术的原发颈部病灶、区域性转移或复发性疾病；远处转移包括纵隔转移；颈部残留病灶不适合再次手术；影像学表现为快速进展或倍增时间 < 6 个月；肿瘤的生长即将造成威胁
生化	不摄取放射性碘或放射性碘治疗疗效不佳；TSH 抑制的情况下（TSH < 0.1 mU/L）疾病仍进展；甲状腺球蛋白(thyroglobulin, Tg)倍增时间 < 6 个月
组织学/分子	分化差或侵袭性病理亚型（如柱状、高细胞、靴钉样等）；Ki-67 指数高；高核分裂象计数/肿瘤坏死
临床判断	临床医师认定的其他侵袭性行为

2 ADTC 术后的 MKI-^{131}I 联合治疗

2.1 联合治疗的必要性

ADTC 的标准治疗仍是首选手术，并在术后进行 ^{131}I 治疗及 TSH 抑制治疗[4]。但 ADTC 术后 ^{131}I 治疗面临一些令人担忧的临床问题：①ADTC 术后局部残留病灶及远处转移灶放射性碘难治的风险高，包括病灶不摄碘或摄碘能力不足，存在 ^{131}I 治疗过程中疾病仍然进展的风险[12-14]。②在 ^{131}I 治疗前，需要撤除外源性甲状腺激素制剂以提高内源性 TSH。高 TSH 刺激下存在病灶增长、症状/症状加重的风险。③除摄碘的微小淋巴结转移和微小肺转移可从 ^{131}I 治疗中获得完全缓解外，其他类型的转移灶（更大的病灶/其他部位转移）即便摄碘良好，单独的 ^{131}I 治疗仍无法达到有效控制[4,15-16]。④多次或高累积活度的 ^{131}I 治疗可导致严重不良反应如肺纤维化、骨髓抑制等，并限制了有效病例的再次 ^{131}I 治疗。

解决这些临床问题需要 ^{131}I 联合其他有效的治疗手段，包括局部治疗及全身系统性治疗，尤其是当残留病灶较大、总体肿瘤负荷较重时。MKI 的全身系统性治疗已被证实对 RRDTC 及术前 LADTC 病灶均具有一定的进展控制及缩瘤作用[17-20]，具有潜在的重启/增加摄碘功能的诱导再分化作用[21]。因此，在 ADTC 术后联合应用 MKI 与 ^{131}I 治疗有如下作用：①控制 ^{131}I 治疗准备过程（如等待手术创伤恢复/并发症的控制、增强 CT 对比剂的排出、甲状腺激素制剂停药等）中的疾病进展，尤其是不摄碘病灶；②缩小病灶、降低肿瘤负荷、重启/增加摄碘功能以增加摄碘病灶的 ^{131}I 治疗效果；③因上述作用减少 ^{131}I 治疗次数/累积活度，从而减少 ^{131}I 治疗严重不良反应的发生。

2.2 联合治疗的临床前研究

Suzuki 等[22]利用 DTC 细胞株体外研究发现，仑伐替尼处理后表达钠碘转运体（sodium-iodide symporter, NIS）的细胞摄碘能力明显增强；仑伐替尼和 ^{131}I 可协同抑制 DTC 细胞的集落形成和迁移；在荷瘤模型动物实验中，^{131}I 联合仑伐替尼显著抑制表达 NIS 的 DTC 裸鼠移植瘤的生长；同时，动物体重及健康指标在各治疗组之间差异无统计学意义，表明联合治疗并未增加毒性作用。MKI 的抗血管生成及血管正常化作用可改善肿瘤微环境的乏氧状态，提高肿瘤细胞对辐射治疗的敏感性；辐射增强细胞膜通透性，以增加细胞内仑伐替尼的摄取。这也部分解释了靶碘联合治疗抗肿瘤协同作用的机制[23]。这些研究结果表明，^{131}I 联合仑伐替尼对摄碘 DTC 具有协同治疗作用，为临床应用提供了理论基础。

2.3 联合治疗的临床尝试

Sheu 等[24]报道仑伐替尼联合 ^{131}I 治疗的 2 例 ADTC 病人，均为 PTC 伴不同程度的局部侵犯、区域转移及远处转移。病例 1，症状性脑转移灶在外照射治疗后仍然进展，经仑伐替尼治疗后病灶缩小（MRI 检查显示病灶直径从 2.5 cm 缩小到 1.3 cm），使病人有机会再次接受 ^{131}I 治疗其他摄碘转移灶。病例 2，因存在双肺多发转移，首次术后即启用并持续仑伐替尼治疗，同时先后 3 次 ^{131}I 治疗，影像学（X 线片、CT）及血清学（Tg）检查均证实联合治疗的效果，且病人生活质量明显改善。 Shi 等[25]报道 5 例 ADTC 病人（4 例 FTC、1 例 FTC 合并 PTC）伴不同

范围远处转移(骨、肺、肝、纵隔),在颈部手术后即接受阿帕替尼治疗,(4±1)个月后,4例表现为部分缓解(partial response, PR)、1例疾病进展(progressive disease, PD)[实体肿瘤的疗效评价标准(Response Evaluation Criteria in Solid Tumor, RECIST)1.1];随后经^{131}I治疗,4例PR病人中的3例及1例PD病人肿瘤缩小、最大标准摄取值(standardized uptake value, SUV_{max})值以及血清Tg水平均降低。

除小样本的临床病例报道外,该领域的注册临床研究也正在开展。RESET研究(ClinicalTrials.gov, NTC04858867)是一项单中心、开放标签的Ⅱ期研究,旨在评估短期仑伐替尼治疗对RRDTC恢复放射性碘摄取和潴留的效果,以达到有效的^{131}I治疗[26]。该研究应用重组人TSH刺激下的^{124}I剂量来估算RRDTC病人接受仑伐替尼治疗(6~12周)前、后的病灶吸收剂量以评估其再分化治疗效果;如果病灶吸收剂量>20 Gy,则停用仑伐替尼后进行^{131}I治疗;研究的主要终点是在仑伐替尼治疗后,符合^{131}I治疗条件的RRDTC病人比例。另一项随机、开放标签的临床试验,探索安罗替尼或派安普利单抗联合放射性碘治疗局部晚期或转移性DTC病人的疗效和安全性[27]。在安罗替尼试验组,^{131}I治疗前、后分别进行4个周期和2个周期的安罗替尼治疗,主要研究终点是ORR,次要终点包括生化应答率(biochemistry response rate, BRR)、疾病控制率(disease control rate, DCR)及中位PFS等。上述两项研究尚无相关研究结果报道。Song等[28]开展了一项单臂Ⅱ期临床试验,该试验对入组的局部晚期或转移性DTC病人先使用安罗替尼治疗4周期,经诊断性^{131}I显像证实病灶摄碘的则接受^{131}I治疗。阶段性研究结果显示该序贯治疗方案的ORR为33.33% (95% CI: 4.33~77.72), DCR为83.33% (95% CI: 35.88~99.58), BRR为100% (95% CI: 54.07~100.00),治疗响应时间(time to response, TTR)为6.34个月(95% CI: 5.85~NE),未达到中位PFS的6例病人中2例发生3级不良事件,包括1例因骨转移引起的疼痛和1例药物相关性高血压,初步证实该序贯治疗方案的安全性和有效性。

3 小结与展望

由于缺乏有效的治疗方案,临床情况复杂及预后不良的ADTC管理需要在多学科共同参与下进一步探索,“靶碘联合”治疗方案正越来越受到关注。联合治疗兼顾广谱细胞抑制剂(MKI)和特异性细胞毒性药物(^{131}I)的优势,有望适用于部分病灶摄碘的病人、摄碘病灶^{131}I治疗后仍快速进展者以及因肿瘤负荷高而预期需多次^{131}I治疗者。临床病例报道及临床试验的阶段性研究结果均初步证实“靶碘联合”治疗的有效性及安全性。更多的数据与经验,包括MKI选择、用药时长、联合使用的顺序等还需更多进一步临床研究的结果。

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