

Research progresses in irreversible electroporation for treatment of malignant tumors

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[Abstract] Irreversible electroporation (IRE) technology may induce cell apoptosis without generating thermal effect nor vascular structure injuries through electric fields, which has better therapeutic effect when combining with chemotherapy and/or immunotherapy, hence becoming a new option of treating malignant tumors. The mechanisms of IRE and relative research progresses for treating malignant tumors were reviewed in this article.

[Keywords] irreversible electroporation therapy; ablation techniques

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不可逆电穿孔技术治疗恶性肿瘤研究进展

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[摘要] 不可逆电穿孔(IRE)技术通过施加电场使细胞发生凋亡而不产生热效应、不损伤脉管结构,与化学治疗和/或免疫疗法联合使用时疗效更佳,是治疗恶性肿瘤的新手段。本文就 IRE 技术原理及其治疗恶性肿瘤研究进展进行综述。

[关键词] 不可逆电穿孔疗法; 消融技术

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恶性肿瘤为全球范围内的主要死因,据“2020 全球癌症统计报告”,2020 年全球预计新发病例为 19 292 789 例,粗发病率 247.5/10 万,预计新发死亡病例 9 958 133 例,粗死亡率 127.8/10 万^[1]。随着科技的发展和研究的深入,目前微创治疗已广泛用于治疗人体各部位恶性肿瘤。

传统热消融治疗利用高温使局部组织发生凝固性坏死而达到治疗目的^[2],但在消除病灶的同时可能损伤周围血管、神经等脉管结构而引起一系列并发症^[3]。不可逆电穿孔(irreversible electroporation, IRE)作为更为精准的治疗方式已逐渐用于临床,可补传统热消融治疗的短板,对消融治疗恶性肿瘤具有重要意义。

1 原理及优势

20 世纪中后期,NEUMANN 等^[4]发现,细胞处于外加电场中时,细胞膜上会产生暂时性通道,若外加电场停止,则通道关闭而细胞仍存活,该现象被称为可逆性电穿孔(reversible electroporation, RE);相关技术现已广泛用于细胞及分子生物学领域,如活体细胞质粒导入、活体细胞内基因转移等^[5],亦可用于治疗恶性肿瘤;以 RE 辅助注射单剂量化疗(化疗)药物可增加肿瘤细胞内部化疗药物浓度、增强疗效,具有广阔应用前景^[6-7]。当外加电场强度超过一定阈值时,撤除电场后细胞膜上的通道将继续存在,引起细胞内外渗透压失衡,导致细胞死亡和/或凋亡^[8],此即为 IRE。

基于独特机制,IRE 不损伤缺乏磷脂双分子层的

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细胞外大分子和结缔组织成分,可保持脉管、神经等结构完整,同时不产生明显温度变化、无“热沉效应”影响,即可实施“选择性”消融^[9],显著提高消融效率^[10]。IRE 诱导细胞凋亡而不引起蛋白质变性、不形成组织瘢痕,允许消融区域正常组织完全再生^[8,11]。一项对比 IRE 与射频消融治疗肝细胞癌 (hepatocellular carcinoma, HCC) 的研究^[12]结果显示,IRE 消融后 1 h 内,血浆巨噬细胞迁移抑制因子增加 9.3 倍,高于射频消融疗法,提示 IRE 可促进组织早期修复、加速消融区功能恢复。此外,IRE 还可诱导机体产生免疫反应,增加 CD8+T 细胞及抗肿瘤细胞因子数量,提高机体抗肿瘤免疫应答,提升消融疗效并抑制肿瘤复发^[13-14]。

2 有效性与安全性

大量基础研究已证实 IRE 的有效性。以 IRE 消融肝脏^[11,15-16]、胰腺^[17-18]、肾脏^[19-20]及前列腺^[21]等肿瘤的动物模型,结果显示消融区域与非瘤组织分界清晰,病灶周围血管、胆管、胰管、输尿管及神经等均未见明显损伤。此外,IRE 对脏器功能仅产生短暂影响,较短时间内可见组织完全再生。动物实验研究^[22-23]结果显示,以 IRE 消融猪甲状腺局部后,甲状腺仅轻度水肿,未见气管、食管及周围肌肉损伤;组织学检查未发现消融灶边缘神经受损,甲状腺及甲状旁腺功能亦无明显变化。

以 IRE 消融治疗肝脏恶性肿瘤的临床研究^[24]显示其成功率为 94.9%,与常规射频消融(96.0%)相当。一项多中心研究^[25]对接受 IRE 消融的 149 例肝肿瘤患者进行随访分析,其中 HCC 患者的中位总生存期(overall survival, OS)为 35 个月,结直肠癌肝转移(colorectal cancer liver metastases, CRCLM)患者中位 OS 为 27 个月;治疗后 30 天内 22 例(14.77%)出现 Clavien-Dindo1-3a 级并发症,低于 VERLOH 等^[26]报道的微波消融/射频消融治疗(29.9%)。SPIERS 等^[27]通过系统分析经 IRE 治疗的 180 例 CRCLM 患者得出相似结果。IRE 消融可延长胰腺癌患者生存期,使其中位 OS 达 10~30 个月^[28];IRE 相关并发症发生率为 25%,常见者包括一过性胰腺炎、胃肠道出血及腹腔积液等,明显低于胰腺切除术相关不良事件(39%)^[29]。WANG 等^[30]以 IRE 治疗肾肿瘤,对所有病灶均实现完全消融,且肾小球滤过率无显著变化,随访 6 个月未见复发。另有研究^[31]表明 IRE 治疗前列腺癌对泌尿生殖功能的损害较小。BLAZEWSKI 等^[32]报道,IRE 消融前列腺癌病灶前、后,患者泌尿功能无显著差异。岳文文等^[33]以 IRE 消

融治疗 12 例甲状腺微小乳头状癌(papillary thyroid microcarcinoma, PTMC),均一次完全消融成功,未见出血、喉返神经损伤及心律失常等严重并发症,术后 6 个月未见复发及转移;为治疗甲状腺癌提供了新的选择。

3 IRE 免疫效应与联合治疗

大量研究发现 IRE 可引发机体强大的免疫应答。GUO 等^[34]以 IRE 消融小鼠 HCC 模型,发现消融后消融区域 CD8+T 细胞浸润程度显著增加、血清 IFN- γ 水平明显升高;DAI 等^[35]向经 IRE 治疗的肝肿瘤模型小鼠二次接种同种癌细胞,之后 30 天内未见新发肿瘤灶,证实 IRE 可抑制肿瘤进展,可能与 IRE 可减少局部及脾脏中的调节性 T 细胞和 PD-1+T 细胞、减轻免疫抑制有关。IRE 通过增加损伤相关分子模式(damage-associated molecular patterns, DAMP)分子合成及其分泌而诱导肿瘤细胞免疫原性死亡,对于抑制肿瘤具有重要作用^[36]。

IRE 与免疫药物相结合,不仅可消除原发肿瘤灶,还可作用于未经治疗的远处转移癌,展现出强大的协同作用潜力,可诱导持久抗肿瘤反应^[37]。MA 等^[38]通过以吉西他滨(Gemcitabine, GEM)单独或联合 IRE 治疗 68 例局部晚期胰腺癌(locally advanced pancreatic cancer, LAPC),相比单独 GEM 组,GEM+IRE 组患者中位 OS(19.8 个月 vs. 9.3 个月)及无进展生存期(progression free survival, PFS)(8.3 个月 vs. 4.7 个月)均明显延长。IRE+化疗用于肝门部胆管癌均较单纯化疗更优,其完全缓解率分别为 52.2%及 12.5%、局部肿瘤进展率分别为 16.7%及 39.5%、局部肿瘤进展时间分别为 11.2 个月及 4.2 个月,患者中位 OS 分别为 19.6 个月及 10.2 个月^[39]。相比 IRE+化疗,IRE+化疗+PD-1/PD-L1 抑制剂治疗 LAPC 后,患者中位 OS(23.6 个月 vs. 19.4 个月)及中位 PFS(18.2 个月 vs. 14.7 个月)均明显上升,提示其可增强抗癌免疫力^[40]。

4 挑战及展望

IRE 因其独特优势而备受瞩目,但其临床应用仍面临巨大挑战。

首先,IRE 作用机制尚未完全明了。有研究^[9,41]发现 IRE 电极针周围组织存在热损伤,热效应与电场强度、电极数量等相关。对于几何形状复杂及特殊部位肿瘤,IRE 消融后易存在残留肿瘤组织;如何精准放置电极针、合理设置参数亦是 IRE 消融的难点。

其次,仍需探索如何规避 IRE 严重并发症。置入

IRE 消融电极针过程可引发气胸、出血等；电脉冲可引起心律失常及肌肉强烈收缩。研究^[28]报道, IRE 消融治疗局部胰腺癌严重并发症发生率为 12%, 2% 的患者死亡与治疗相关。

再次, IRE 相关免疫反应及联合应用相关基础研究结果存在差异^[42]; 而临床研究往往存在选择偏倚, 缺乏大规模随机对照试验及长期随访研究, 且 IRE 消融后影像学变化与组织学和细胞学改变的相关机制仍未明确。需开展大量基础及临床研究以优选消融参数、规范消融流程; 正确评价 IRE 消融后肿瘤组织和非瘤组织, 制定重要结构保护标准, 深入探索联合治疗的作用机制及其最佳组合。已有研究^[17]表明, 利用高频 IRE 可有效避免心律失常及肌肉收缩; 相关产品有待进一步研发。

5 小结

IRE 用于消融治疗恶性肿瘤具有良好的有效性与安全性, 临床价值及发展空间巨大; 通过不断深入研究并进一步发展、完善, IRE 将在治疗恶性肿瘤中发挥更大作用。

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