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马骏, 中国科学院院士。擅长放射肿瘤学及鼻咽癌的临床诊治, 创立了鼻咽癌临床分期新标准及增效减毒治疗新策略。研究论文在*NEJM*、*Lancet*、*JAMA*、*BMJ*、*CA*等期刊上发表。曾获国家科技进步二等奖3项、中华医学科技一等奖3项、高等学校科技进步一等奖2项、中国高等学校十大科技进展2项、中国科协生命科学十大进展、中国医学科学院中国医学重大进展2项等奖项。

增效与减毒: 局部晚期鼻咽癌的治疗进展

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摘要　调强放射治疗(intensity-modulated radiation therapy, IMRT)作为鼻咽癌(nasopharyngeal carcinoma, NPC)的根本治疗方式, 可显著提高肿瘤的局部控制率。然而, 远处转移仍是治疗失败的主要原因。近年来, 多项大型临床试验证实, 化疗结合IMRT可提高高危局部晚期鼻咽癌患者的生存率, 其中, 诱导化疗和节拍辅助化疗以其确切的增效作用和良好的患者耐受性已成为目前指南推荐的首选治疗模式。此外, 随着患者生存期的延长, 保证其生活质量尤为重要。在鼻咽癌减毒治疗方面, 化疗豁免、选用低毒等效化疗药物以及选择性豁免低危淋巴结区域预防性放疗等治疗策略能够在维持疗效的同时, 显著提高患者的生活质量。免疫治疗近期已成为局部晚期鼻咽癌治疗的研究热点, 显示出进一步增效的能力, 其与放化疗结合的最佳时机和方案仍需进一步确定。

关键词　鼻咽癌; 诱导化疗; 节拍化疗; 免疫抑制剂; 选择性照射

Enhancing Efficacy and Reducing Toxicity: Therapeutic Optimization in Locoregionally Advanced Nasopharyngeal Carcinoma

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Abstract IMRT (intensity-modulated radiation therapy) has emerged as the fundamental treatment modality for NPC (nasopharyngeal carcinoma), significantly improving local control rates and patient survival. However, distant metastasis remains the primary cause of treatment failure. Recent large-scale clinical trials have demonstrated that combining systemic chemotherapy with IMRT can enhance survival rates in high-risk patients with locoregionally advanced NPC. Notably, induction chemotherapy and metronomic adjuvant chemotherapy, due to their significant efficacy and favorable patient tolerance, have become the preferred treatment regimens recommended in international guidelines. Moreover, as survival extends, maintaining patients' quality of life becomes increasingly important. Recent advancements in toxicity reduction strategies for NPC has shown enhanced patients' quality of life while preserving treatment efficacy. These strategies include chemotherapy exemptions, the adoption of low-toxicity, equivalent chemotherapy agents, and the exemption of low-risk lymph node regions from prophylactic irradiation. Furthermore, immunotherapy has emerged as a research hotspot in the treatment of locoregionally advanced NPC, demonstrating its ability to enhance treatment outcomes. Further research is needed to determine the optimal timing and regimen for its integration with chemoradiotherapy.

Keywords nasopharyngeal carcinoma; induction chemotherapy; metronomic chemotherapy; immune checkpoint inhibitors; elective irradiation

鼻咽癌(nasopharyngeal carcionoma, NPC)是起源于鼻咽黏膜的恶性肿瘤, 具有地域高发特点, 主要累及我国华南地区及东南亚人群[1]。根据世界卫生组织的分类, 鼻咽癌可分为三种组织学类型: 角化性鳞状细胞癌、非角化性癌及基底样鳞状细胞癌。其中, 非角化性癌下分为未分化型与分化型两个亚型[2]。在高发地区, 超过95%的鼻咽癌病理类型为未分化型非角化性癌[3], 这一亚型通常与EB病毒(Epstein-Barr virus, EBV)的慢性潜伏感染相关[4], 并且具有较强的侵袭能力, 易发生远处转移。

由于鼻咽部毗邻颅底, 解剖位置隐匿, 且对射线较为敏感, 因此鼻咽癌的主要治疗手段是放射治疗。调强放射治疗(intensity-modulated radiation therapy, IMRT)以其与肿瘤靶区轮廓高度适形的特点, 可以实现对原发病灶的精准靶向, 提高肿瘤局部控制率, 减少对周围正常组织的损伤, 现已成为非转移性鼻咽癌的主要治疗模式[5]。如今, 对于早期鼻咽癌, 仅接受单纯调强放疗的患者5年无局部复发生存率及无转移生存率均已超过95%[6]。然而, 对于局部晚期鼻咽癌患者, 初诊时较高的肿瘤分期及常见的未分化型病理类型使得患者远处转移风险增加, 仅接受局部放射治疗的局部晚期患者5年总生存率小于50%[7-8]。

由于影像诊断技术及放射治疗技术的革新, 鼻咽癌的局部控制率已显著提升, 如今局部晚期鼻咽癌治疗失败的主要原因是远处转移[9]。近年来, 大量研究聚焦于将化疗与放疗结合以进一步提高疗效。同期放化疗结合诱导化疗或辅助化疗的治疗方式显著改善了局部晚期患者的生存结局。

1 最佳化疗时机

Intergroup 0099研究是证实放化联合治疗在晚期鼻咽癌患者中可提高生存率的重要里程碑研究[7]。该研究显示, 相比于单纯放疗, 在放疗基础上增加以顺铂为基础的同期化疗及三周期顺铂-5-氟尿嘧啶(cisplatin-5-fluorouracil, PF)辅助化疗将晚期鼻咽癌患者的5年总生存率和无进展生存率分别提高了31%和45%(5年总生存率47% *vs* 78%; 5年无进展生存率24% *vs* 69%)。后续在鼻咽癌高发地区的系列研究进一步证实了这一结论[10-12], 使同期放化疗结合辅助化疗成为自1990年代末以来局部晚期鼻咽癌的标准治疗方案。

尽管化疗在局部晚期鼻咽癌中的生存获益已被广泛认可, 但最佳的化疗时机仍不明确。同期化疗在提高局部晚期鼻咽癌生存率方面的有效性已在多项临床试验得到证实[13-15], 然而, 对于辅助化疗对生存结局的意义, 回顾性研究和荟萃分析得出了不一致的结论[16-19]。值得注意的是, 迄今为止最大的一项直接比较同期放化疗与同期放化疗结合辅助化疗在局部晚期鼻咽癌中疗效的III期临床试验显示[15,20], 与仅同期放化疗相比, 同期放化疗联合PF辅助化疗未能显著提高患者的2年及5年无失败生存率和总生存率。此外, 2018年的一项随机III期临床

试验结果显示, 吉西他滨–顺铂(gemcitabine-cisplatin, GP)方案的辅助化疗在高危晚期鼻咽癌患者中也未有额外的生存获益[21]。

辅助化疗在提高疗效方面的作用较为有限, 这可能是因为患者在接受了根治性放化疗后对传统辅助化疗方案的耐受性降低(不同试验中的依从率仅为50%至66%[7,15,21-23])。此外, 对于存在目前检测手段未能检出的全身微小转移灶的患者, 在标准的7周放疗结束后增加化疗, 可能未能及时阻止微小转移灶的进展和扩散。

基于上述因素考虑, 诱导化疗可能是更为有效的治疗方式。在治疗过程中早期应用全身化疗可能更有效地消除微小转移灶, 提高患者对综合放化疗的耐受性, 并减少肿瘤负荷, 缩小放疗靶区, 减少放疗副反应。目前, 局部晚期鼻咽癌的诱导化疗方案主要为以顺铂为基础的双药或三药联合方案[24], 包括GP、多西他赛–顺铂-5-氟尿嘧啶(docetaxel-cisplatin-5-fluorouracil, TPF)、PF、顺铂–卡培他滨(cisplatin-capecitabine, PX)和多西他赛–顺铂(docetaxel-cisplatin, TP)等方案。这些方案可提高局部晚期鼻咽癌生存率的有效性已在多项临床试验中得到证实[25-30](表1)。此外, 来自中国台湾的一项III期临床试验结果显示, 丝裂霉素、表柔比星、顺铂、5-氟尿嘧啶和亚叶酸(mitomycin, epirubicin, cisplatin, 5-fluorouracil, and leucovorin, MEPFL)诱导化疗方案能够显著提高IVA和IVB期鼻咽癌患者的5年无病生存率(61% *vs* 50%; 风险比[hazard ratio, HR] 0.74; 95%置信区间[confidence interval, CI] 0.57-0.97; *P*=0.026 4), 然而其总生存率未得到显著提高[31](表1)。由于目前缺乏不同诱导化疗方案间的对比研究, 临床实践中诱导化疗方案的选择应根据患者的具体情况而定。然而, 根据临床研究证据等级, 2024年美国国家综合癌症网络(National Comprehensive Cancer Network, NCCN)指南将TPF和GP诱导化疗方案推荐为局部晚期鼻咽癌的首选方案[32], 在EBV相关鼻咽癌的治疗中, TPF和GP诱导化疗方案均有1级临床证据等级支持。

1.1 TPF诱导化疗: 局部晚期鼻咽癌的诱导化疗首选方案

基于TPF诱导化疗方案在头颈鳞状细胞癌中的疗效[39-40], 其在鼻咽癌中的应用得到广泛探索。2010年的一项I期临床试验显示, TPF诱导化疗在局部晚期鼻咽癌中的总体应答率为90%, 完成诱导化疗及放疗后, 患者的应答率高至97.5%[41]。随后进行的两项II期临床试验显示, 应用TPF诱导化疗可将晚期鼻咽癌患者的3年总生存率提升至81.8%~94.8%, 且患者耐受性良好[42-43]。后续在鼻咽癌高发地区开展的一项大规模III期临床试验进一步证实了TPF诱导化疗的疗效[26], 该试验纳入了480名局部晚期鼻咽癌患者(不包括T3-4N0), 随机接受同期放化疗或TPF诱导化疗+同期放化疗(表1)。结果显示, TPF诱导化疗组的3年无病生存率、总生存率和无远处失败生存率分别为80%、92%和90%, 显著优于同期放化疗组(72%、86%和83%; HR及95% CI分别为0.68 [0.48-0.97]、0.59 [0.36-0.95]和0.59 [0.37-0.96])。值得注意的是, 加入TPF诱导化疗使患者的远处转移风险降低了41%。2018年, 一项来自突尼斯和法国的III期临床试验进一步确证了TPF诱导化疗的疗效[34](表1): TPF诱导化疗显著提高了局部晚期鼻咽癌患者的3年无进展生存率(73.9% *vs* 56.2%; HR 0.44, 95% CI 0.20-0.97; *P*=0.042), 且总生存率也略有改善(86.3% *vs* 68.9%; HR 0.40, 95% CI 0.15-1.04; *P*=0.05)。

基于上述发现, NCCN指南在2018年将TPF诱导化疗纳入了鼻咽癌的全身治疗推荐, 并将诱导化疗结合同期放化疗这一治疗模式的证据等级从3提升至2A[44], 强调了诱导化疗在局部晚期鼻咽癌治疗中的重要性。

1.2 GP诱导化疗: 高效低毒, 成为局部晚期鼻咽癌的标准治疗方案

GP化疗方案在包括头颈肿瘤在内的多个实体瘤中展现出了显著疗效[45-46]。在鼻咽癌中, 两项II期临床试验显示, GP化疗方案在复发/转移性鼻咽癌患者中具有良好的应答率及可控的安全性[47-48]。2016年一项大型III期临床试验证实[49], 对于复发/转移鼻咽癌患者, GP化疗在无进展生存期方面显著优于PF方案(7.0 *vs* 5.6个月; HR 0.55, 95% CI 0.44-0.68; *P*<0.000 1), 因此, GP方案取代了PF化疗方案成为复发/转移性鼻咽癌的一线治疗首选方案。

对于局部晚期鼻咽癌患者, 2019年一项大型多中心III期临床试验结果显示, GP诱导化疗结合同期放化疗在局部晚期鼻咽癌患者中具有显著疗效, 且患者耐受性良好(表1)[25]。该试验纳入了480名III至IVB期鼻咽癌患者, 按1:1比例随机分为接受GP诱导化疗加同期放化疗组或仅同期放化疗组。GP诱导化疗的具体方案为化疗第1天和第8天按1 g/m²体表

表1 近期主要评估诱导化疗、辅助化疗或二者联合放疗在局部晚期鼻咽癌中有阳性结果的III期临床试验

Table 1 Recent main phase III trials evaluating IC, AC, or both with positive results for locoregionally advanced NPC management

研究 Study	实验组化疗 Experimental chemotherapy	对照组化疗 Control chemotherapy	样本量 Sample size	总生存率 OS (experimental *vs* control; HR [95% CI]; *P*)	主要终点 Primary endpoint (experimental *vs* control; HR [95% CI]; *P*)	意义 Significance
SUN et al[26] 2016 LI et al[33] 2019	IC: docetaxel 60 mg/m^2 d1, cisplatin 60 mg/m^2 d1, fluorouracil 600 mg/m^2 d1-5, q3wks × 3; CCT: cisplatin 100 mg/m^2 d1, q3wks × 3	CCT: cisplatin 100 mg/m^2 d1, q3wks × 3	480	5-year: 85.6% *vs* 77.7%; 0.65 (0.43-0.98); *P*=0.042	5-year FFS: 77.4% *vs* 66.4%; 0.67 (0.48-0.94); *P*=0.019 0	Established TPF IC as a first-line treatment option for locoregionally advanced NPC
CAO et al[29] 2017 YANG et al[30] 2019	IC: fluorouracil 800 mg/m^2 d1-5, cisplatin 80 mg/m^2 d1, q3wks × 2; CCT: cisplatin 80 mg/m^2 d1, q3wks × 3	CCT: cisplatin 80 mg/m^2 d1, q3wks × 3	476	5-year: 80.8% *vs* 76.8%; 0.69 (0.49-0.98); *P*=0.040	5-year DFS: 73.4% *vs* 63.1%; 0.66 (0.48-0.89); *P*=0.007; 5-year DMFS: 82.8% *vs* 73.1%; 0.61 (0.41-0.91); *P*=0.014 0	Demonstrated PF regimen as an effective IC regimen option
FRIKHA et al[34] 2018 (GORTEC 2006-02)	IC: docetaxel 75 mg/m^2 d1, cisplatin 75 mg/m^2 d1, fluorouracil 750 mg/m^2 d1-5, q3wks × 3; CCT: cisplatin 40 mg/m^2, q1wk	CCT: cisplatin 40 mg/m^2, q1wk	83	3-year: 86.3% *vs* 68.9%; 0.40 (0.15-1.04); *P*=0.050	5-year PFS: 73.9% *vs* 57.2%; 0.44 (0.20-0.97); *P*=0.042 0	Validated the efficacy of TPF IC for locoregionally advanced NPC in less endemic regions
HONG et al[31] 2018 (TCOG)	IC: mitomycin 8 mg/m^2 d1, epirubicin 60 mg/m^2 d1, cisplatin 60 mg/m^2 d1, fluorouracil 450 mg/m^2 d8, leucovorin 30 mg/m^2 d8, q3wks × 3; CCT: cisplatin 30 mg/m^2 d1, q1wk	CCT: cisplatin 30 mg/m^2 d1, q1wk	479	5-year: 72% *vs* 68%; 0.92 (0.67-1.27); *P*=0.624	5-year DFS: 61% *vs* 50%; 0.74 (0.57-0.97); *P*=0.026 4	Suggested the MEPFL regimen as a potential viable IC option for locoregionally advanced NPC
ZHANG et al[25] 2019 ZHANG et al[35] 2022	IC: gemcitabine 1 000 mg/m^2 d1,8, cisplatin 80 mg/m^2 d1, q3wks × 3; CCT: cisplatin 100 mg/m^2 d1, q3wks × 3	CCT: cisplatin 100 mg/m^2 d1, q3wks × 3	480	5-year: 87.9% *vs* 78.8%; 0.51 (0.34-0.78); *P*=0.001	5-year FFS: 81.3% *vs* 67.3%; 0.51 (0.36-0.73); *P*<0.001 0	Established GP IC as the standard treatment regimen for locoregionally advanced NPC
LEE et al[36] 2015 LEE et al[28] 2020 (NPC0501)	IC: capecitabine 2 000 mg/m^2/day p.o. for 14 days or fluorouracil 1 000 mg/m^2/day for 120 hours, cisplatin 100 mg/m^2, q3wks × 3; CCT: cisplatin 100 mg/m^2, q3wks × 2-3	CCT: cisplatin 100 mg/m^2, q3wks × 2-3; AC: cisplatin 80 mg/m^2, fluorouracil 1 000 mg/m^2/day for 96 hours, q4wks × 3	293	5-year: 83.6% *vs* 71.9%; *P*=0.042 (the conventional-fractionation group)	5-year PFS: 77.6% *vs* 61.5%; *P*=0.015 0 (the conventional-fractionation group)	Suggested the PX regimen as an effective and convenient IC regimen option
CHEN et al[37] 2021	CCT with or without IC followed by AC: metronomic capecitabine 650 mg/m^2 bid, p.o., d1-21, q3wks, continued until disease progression, unacceptable toxicity, or over 1 year	CCT with or without IC followed by observation	406	3-year: 93.3% *vs* 88.6%; 0.44 (0.22-0.88); *P*=0.018	3-year FFS: 85.3% *vs* 75.7%; 0.50 (0.32-0.79); *P*=0.002 3	Established metronomic chemotherapy as a new, efficacious, affordable, minimally toxic, and well-tolerated AC approach in high-risk patients with NPC

续表1

研究 Study	实验组化疗 Experimental chemotherapy	对照组化疗 Control chemotherapy	样本量 Sample size	总生存率 OS (experimental *vs* control; HR [95% CI]; *P*)	主要终点 Primary endpoint (experimental *vs* control; HR [95% CI]; *P*)	意义 Significance
MIAO et al[38] 2022	CCT followed by full-dose capecitabine AC: 1 000 mg/m^2, bid, p.o., d1-14, q3wks for eight cycles	CCT	180	3-year: 93.3% *vs* 87.8%; 5-year: 87.8% *vs* 82.1%; 0.62 (0.29-1.32)	3-year: 83.3% *vs* 72.2%; 5-year: 78.5% *vs* 65.9%; 0.53 (0.30-0.94); *P*=0.030	Suggested full-dose capecitabine as a potential viable AC option

OS: 总生存率; IC: 诱导化疗; AC: 辅助化疗; NPC: 鼻咽癌; HR: 风险比; CI: 置信区间; CCT: 同期化疗; FFS: 无失败生存率; TPF: 多西他赛–顺铂-5-氟尿嘧啶; DFS: 无病生存率; DMFS: 无远处转移生存率; PF: 顺铂-5-氟尿嘧啶; PFS: 无进展生存率; MEPFL: 丝裂霉素–表柔比星–顺铂-5-氟尿嘧啶–亚叶酸; PX: 顺铂–卡培他滨; GP: 吉西他滨–顺铂; q3wks: 每3周; q1wk: 每1周; d1: 第1天; q4wks: 每4周; bid: 每日两次; p.o.: 口服给药。
OS: overall survival; IC: induction chemotherapy; AC: adjuvant chemotherapy; NPC: nasopharyngeal carcinoma; HR: hazard ratio; CI: confidence interval; CCT: concurrent chemotherapy; FFS: failure-free survival; TPF: docetaxel, cisplatin, and fluorouracil; DFS: disease-free survival; DMFS: distant metastasis-free survival; PF: cisplatin and fluorouracil; PFS: progression-free survival; MEPFL: mitomycin, epirubicin, cisplatin, fluorouracil, and leucovorin; PX: cisplatin and capecitabine; GP: gemcitabine and cisplatin; q3wks: every 3 weeks; q1wk: every 1 week; d1: day1; q4wks: every 4 weeks; bid: twice a day; p.o.: oral administration.

面积静脉滴注吉西他滨, 化疗第1天按80 mg/m²体表面积静脉滴注顺铂, 每3周为1个周期, 共3周期。同期化疗方案为在第1、22、43天按100 mg/m²体表面积静脉滴注顺铂, 间隔3周。结果显示, GP诱导化疗组的3年无复发生存率显著优于仅同期放化疗组(85.3% *vs* 76.5%; HR 0.51, 95% CI 0.34-0.77; *P*=0.001)。此外, GP诱导化疗组的无远处复发生存率(91.1% *vs* 84.4%; HR 0.43, 95% CI 0.25-0.73)和5年总生存率(87.9% *vs* 78.8%; HR 0.51, 95% CI 0.34-0.78; *P*=0.001)分别提高了6.7%和9.1%[35]。值得注意的是, 两个组的局部无复发生存率相近(GP诱导化疗组为91.8% [95% CI 87.3-94.7], 仅同期放化疗组为91.0% [95% CI 86.2-94.0]), 这表明GP诱导化疗的生存优势主要与其对远处转移的控制有关。

在显著提高疗效之余, 患者对GP诱导化疗方案展现出了较好的耐受性。三周期GP诱导化疗的完成率为96.7%, 3级或4级中性粒细胞减少、白细胞减少和腹泻的发生率分别为20.5%、10.9%和0.4%。此外, 与TPF诱导化疗方案相比, GP诱导化疗在4级不良事件的发生率上减少了近三分之二[26], 尤其是4级中性粒细胞减少、白细胞减少和血小板减少, 这提示其在维持骨髓造血功能方面可能更有优势。

鉴于GP诱导化疗方案的显著疗效和良好的安全性, 诸多国际指南已将GP诱导化疗联合同期放化疗推荐为局部晚期鼻咽癌的标准治疗方案[32,50-51]。

对于GP方案在治疗鼻咽癌中的具体机制, LÜ等[52]研究发现, 除了作为化疗药物直接的细胞毒性作用外, GP化疗还通过激活以ILB(innate-like B)细胞为主导的免疫反应, 增强抗肿瘤免疫, 实现高效杀伤肿瘤的作用。ILB细胞主要经由GP化疗通过TLR9通路诱导, 存在于肿瘤免疫微环境中的类三级淋巴结构(tertiary lymphoid organ-like structures)中。作为抗原呈递细胞, ILB通过ICOSL-ICOS信号轴激活mTOR通路, 促进滤泡辅助性T细胞(follicular helper T cells, Tfh)和1型辅助性T细胞(helper type-1 T cells, Th1)的扩增, 进而增强细胞毒性T淋巴细胞的肿瘤杀伤功能。该研究还显示, ILB是GP化疗在鼻咽癌中疗效的独立预测因子, 具有指导化疗方案选择的应用价值。

尽管诱导化疗在局部晚期鼻咽癌中展现出显著疗效, 仍有23.7%~32.6%的患者在诱导化疗结束时检测出持续存在的EBV DNA[53-54], 这与生存率显著降低相关[55]。两项回顾性研究显示, 对于诱导化疗抵抗的患者, 使用其他化疗方案重新进行诱导或在同期化疗时采用双药化疗的疗效均不理想[56-57]。对于这部分患者, 目前在研的治疗策略包括: 延长诱导化疗周期并同时应用PD-1抑制剂(NCT04072107)、节拍辅助化疗(NCT05517135), 或二者联合治疗(NCT05628922)。这些研究的结果可能为诱导化疗抵抗患者的治疗提供新的启示。

2 节拍辅助化疗: 高危鼻咽癌高效维持治疗新选择

尽管诱导化疗联合同期放化疗显著改善了局

部晚期鼻咽癌患者的生存结局, 仍有约25%的患者可能出现肿瘤复发或转移[25,58], 因此需要有效的辅助维持治疗手段降低复发转移及死亡风险。然而, 正如前文所述, 同期放化疗基础上增加辅助化疗的有效性仍存在争议, 而影响疗效的重要原因是同期放化疗后患者对传统顺铂方案的耐受性降低。

卡培他滨在局部晚期鼻咽癌治疗中作为静脉输注5-氟尿嘧啶的替代方案, 展现出较低的毒性和与之相近的疗效[36]。在复发/转移性鼻咽癌中, 卡培他滨单药治疗也显示出良好的治疗效果[59]。近期一项随机III期临床试验探索了全剂量卡培他滨(1 000 mg/m² 体表面积, 每日两次, 服用14天, 间隔21天为一周期, 共八周期)作为局部晚期鼻咽癌辅助化疗的疗效[38], 结果显示, 与仅同期放化疗相比, 卡培他滨辅助化疗显著提高了患者3年及5年无失败生存率(83.3% *vs* 72.2%及78.5% *vs* 65.9%; HR 0.53, 95% CI 0.30-0.94; *P*=0.03; 表1), 且患者依从性良好。因此, 全剂量卡培他滨辅助化疗可能是局部晚期鼻咽癌的可行治疗方案之一。

节拍化疗是指在不进行长时间停药的情况下, 以远低于常规的化疗药物剂量, 频繁、规律地给药。其优势在于毒性较低、患者依从性良好[60]。除了化疗药物的直接细胞毒性作用外, 其抗肿瘤机制还包括抑制血管生成、调节免疫反应以及对肿瘤干细胞的直接靶向作用[61]。在鼻咽癌中, 节拍辅助化疗是近来针对高危局部晚期鼻咽癌的高效维持治疗新选择。

回顾性研究显示, 使用口服5-氟尿嘧啶类似物作为节拍辅助化疗能显著降低高危患者的疾病复发率[62-64]。近期一项多中心、随机、III期临床试验评估了节拍卡培他滨辅助化疗在高危局部晚期鼻咽癌患者中的疗效和安全性[37], 该试验的研究对象为406名III至IVA期鼻咽癌患者(排除T3-4N0和T3N1; 表1)。患者被随机分为接受口服节拍辅助卡培他滨组(650 mg/m²体表面积, 每日两次, 持续1年)或观察组(标准治疗组)。标准治疗方案为同期放化疗联合或不联合诱导化疗。结果显示, 标准治疗后进行节拍卡培他滨辅助治疗能够显著提高患者的3年无失败生存率、总生存率、无远处失败生存率和局部区域无失败生存率(分别为85.3% *vs* 75.7%、93.3% *vs* 88.6%、82.1% *vs* 89.4%和87.8% *vs* 92.6%; HR [95% CI]分别为0.50 [0.32-0.79]、0.44 [0.22-0.88]、0.52 [0.30-0.88]和0.50 [0.25-0.98]; *P*值分别为0.002 3、0.018 0、0.014 0和0.041 0)。值得注意的是, 增加节拍辅助卡培他滨治疗将患者的复发转移或死亡风险降低了50%。

在安全性方面, 节拍辅助卡培他滨的主要不良事件为手足综合征。3级不良事件的发生率为17%, 相比常规PF辅助化疗方案降低了25%[15]。仅有1例患者(<1%)报告发生了4级不良事件。此外, 节拍辅助卡培他滨未对患者的生活质量产生显著负面影响。

这些结果表明, 节拍辅助化疗是一种高效、低毒、经济的高危鼻咽癌维持治疗新模式。此外, 上述两项卡培他滨辅助化疗的研究结果还提示, 相比于传统化疗方案, 更为温和的辅助治疗方案, 如口服卡培他滨或免疫检查点抑制剂, 可能更适用于局部晚期鼻咽癌的辅助治疗。

3 减毒治疗: 向精准医疗迈进

IMRT联合化疗显著改善了局部晚期鼻咽癌患者的治疗结局, 使其5年总生存率超过了85%[33,35]。然而, 对于低危患者而言, 显著增加的治疗强度可能导致过度治疗, 增加不必要的不良反应风险。单纯放疗即可引发一系列不良反应, 包括放射性皮肤反应、口腔黏膜炎、吞咽困难、口干和听力下降等[65]。在此基础上增加全身化疗不仅使这些不良事件的风险增高, 还可能发生骨髓抑制等其他化疗相关副反应[66]。随着生存期的延长, 患者的生活质量愈发重要。

近年来, 鼻咽癌治疗研究的另一重点在于如何在保持或增加治疗效果的同时, 尽可能减少放化疗毒性。其中, 精准的风险分层尤为重要, 对高危与低危患者的准确区分有助于合理分配治疗强度。具有高预测价值的解剖和分子标志物的临床应用, 有望提升鼻咽癌的个体化治疗水平。此外, 几项大规模临床试验已证实, 对低危患者进行降强度治疗是安全可行的。同时, 对鼻咽癌颈部淋巴结转移规律的深入研究, 推动了预防性照射范围的优化。这些进展促进了鼻咽癌精准治疗的发展。

3.1 分期系统的改进

国际抗癌联盟(Union for International Cancer Control, UICC)/美国癌症联合委员会(American Joint Committee on Cancer, AJCC)制定的TNM分期系统是

评估肿瘤进展、预测疾病预后以及指导治疗选择的公认标准。早期UICC/AJCC鼻咽癌分期系统的制定主要基于欧美人群的研究, 而高发地区则采用各自指南[67-68]。自第七版TNM分期(TNM-7)起, UICC/AJCC鼻咽癌分期系统采纳了以中国大陆高发地区为主的国际研究成果, 极大地推动了第七版和第八版TNM分期(TNM-7和TNM-8)的更新[69-71]。据估计, 自TNM-7更新后, 约30%的患者得到了更准确的分期和相应治疗[72]。在预后区分方面, 总体分期及相邻N分期的生存曲线展现出了更为显著的差异[71-72]。

然而, 目前的TNM-8鼻咽癌分期系统仍存在一定局限性。在T分期方面, T2和T3分期患者的生存曲线有部分重叠[73]。对颅底骨质精细解剖结构的研究发现, T3患者若仅有早期颅底骨质受侵(仅侵犯蝶骨基底部和/或翼突), 其预后与T2患者相似[74-76], 提示T分期相应调整的必要性。在N分期方面, 对于影像学所见具有颈部淋巴结高级别包膜外侵(advanced extrnodal extension, 明确累及邻近肌肉、皮肤和/或神经血管结构, 即3级淋巴结包膜外受侵, grade 3 image-identified extranodal extension, G3-iENE)的患者, 尽管经过强化治疗, 仍具有较高的远处转移风险[77-78]。将颈部淋巴结高级别包膜外侵纳入N分期相比于单独使用TNM-8分期, 能够更好地预测患者的预后[79-80]。此外, 对于M1期患者, 转移灶的数量和解剖位置是重要的预后因素[81-82], 需进一步进行风险分层。

综合上述研究进展, DU等[83]展开了一项针对EBV相关鼻咽癌TNM-8临床分期修订的研究, 该研究基于多中心共8 334例初诊非转移性鼻咽癌患者及939例初诊转移性鼻咽癌患者, 提出了分期修订建议, 构建了新版分期模型, 包括: 将T3分期中的早期颅底骨质受侵由T3降为T2; 将颈部淋巴结高级别包膜外侵升级到N3; 将非转移性鼻咽癌分为I-III期, 其中T1N0及T2N0合并为IA期, T1-2N1为IB期, 原III期降为II期, 原IVA期降为III期; 转移性鼻咽癌为IV期, 根据是否存在3个以上转移灶及肝转移进一步分为IVA期及IVB期。按照Groome评价标准, 修订后的分期在预后区分度、风险一致性、预后预测效能、样本均衡性方面均优于第八版TNM分期。这些结果表明, 修订后的分期更准确地反映了当前治疗模式下的患者风险特征。基于以上研究, 第九版鼻咽癌TNM分期已将颈部淋巴结高级别包膜外侵升级到N3, 并将总分期相应调整[84]。

尽管对鼻咽癌精细解剖学特征的深入研究使预后预测更为准确, 但在临床实践中, 仍有相同分期、接受相同治疗的患者表现出互不一致的疗效。这种差异可能与肿瘤微环境的生物学异质性相关[85]。因此, 将有预测价值的分子标志物纳入传统仅基于解剖学的分期系统尤为必要。目前, 已有多种分子标志物(如EBV DNA水平、基因表达特征和miRNA)被证实与鼻咽癌治疗的预后密切相关, 其与TNM分期的结合也显示出更高的预后准确性[86-88]。然而, 目前仍缺乏对分子标志物标准化的检测方法。此外, 亦需要在流行地区与非流行地区间进行验证, 以促进其临床应用的推广。

3.2 低危患者的化疗豁免

根据既往NCCN指南, II-IV期鼻咽癌患者的推荐治疗均为同期放化疗±诱导/辅助化疗, 其中, 针对II期患者的同期放化疗推荐证据主要来自二维放疗时期的III期临床试验数据[89]。近年来, IMRT已取代二维常规放疗, 其具有更好的肿瘤靶区适形性、更高的靶区剂量覆盖以及更优的正常组织保护, 明显提高了鼻咽癌疗效。IMRT治疗模式下, II期鼻咽癌患者的无瘤生存、总生存、无远处转移生存及无复发生存均可达到90%以上, 在此基础上, 同期化疗能够带来的生存获益空间则明显减少。同时, 以铂类为基础的同期化疗明显增加了患者的治疗副反应率及治疗相关死亡风险。因此, 在调强治疗模式下, 低危鼻咽癌患者是否仍需要行同期顺铂化疗是亟待解决的科学问题。一项针对440例II期及T3N0M0期鼻咽癌患者的回顾性研究显示, 接受单纯调强放疗组的患者与接受同期放化疗组的患者在3年总生存率、无进展生存率、局部无失败生存率和无远处失败生存率方面并未表现出显著差异[90]。然而, 同期放化疗组患者的3~4级急性毒性反应发生率相比单纯放疗组增加了20%以上。另一项II期多中心试验也表明, 在单纯放疗基础上增加额外的同期化疗未能显著提高II期鼻咽癌患者的生存率, 反而导致了显著的血液学毒性[91]。2022年, TANG等[66]报道了一项在低危鼻咽癌患者中单纯放疗对比同期放化疗的前瞻性、III期、非劣效性临床试验的结果, 该研究将低危患者定义为: II期/T3N0M0期鼻咽患者, 且符合颈部淋巴结直径小于3 cm、无IV-Vb区淋巴结受累、无颈部淋巴结包膜外侵以及EBV DNA水平低于4 000拷贝/mL。该试验结果显示, 单纯放疗组

与同期放化疗组在3年无进展生存率、局部无复发生存率、无远处转移生存率和总生存率方面无显著统计学差异(分别为91.9%、94.3%、97.6%、98.6% *vs* 90.5%、94.0%、95.8%、98.2%, 非劣效P<0.001, P=0.43, P=0.22, P=0.31)。此外, 单纯放疗组的3~4级急性毒性反应发生率降低了30%, 化疗豁免使患者的生活质量得到显著改善。该研究为低危患者豁免同期化疗的治疗策略提供了强有力的证据支持。然而, 目前仍需多中心标准化的低危患者标准, 以进一步推广这一治疗模式。

3.3 奈达铂与洛铂: 顺铂的低毒等效替代方案

以顺铂为基础的同期放化疗是晚期鼻咽癌的标准治疗模式, 尽管显著提高了患者的生存率, 但往往造成较多的毒性反应, 使患者治疗依从性和生活质量降低。奈达铂(nedaplatin)和洛铂(lobaplatin)分别为第二代和第三代铂类药物, 具有较少的副作用和更好的耐受性。多项II期临床试验表明, 奈达铂和洛铂在鼻咽癌治疗的诱导化疗、同期化疗或诱导及同期化疗阶段具有与顺铂相当的治疗效果[92-94]。两项大规模的III期临床试验进一步证实了奈达铂和洛铂在疗效上的非劣效性[95-97], 且二者的毒性均较顺铂更低(表2)。这提示, 对于局部晚期鼻咽癌患者, 基于奈达铂或洛铂的化疗方案可能成为顺铂治疗的低毒替代方案。然而, 奈达铂和洛铂目前在中国以外地区的应用尚不广泛, 仍需进一步开展大规模的国际验证以证实其疗效。

3.4 低危淋巴结区域的放疗豁免

由于鼻咽部淋巴网络丰富, 鼻咽癌患者易于发生区域淋巴结转移。约80%的鼻咽癌患者在初诊时即已出现颈部淋巴结转移[99]。在以体格检查和二维放疗为主要诊疗手段的时期, 为了降低颈部淋巴结区域复发的风险, 无论患者是否出现颈淋巴结转移, 放射治疗范围均为全颈覆盖照射[100]。然而, 广泛的放疗范围不可避免地对周围正常结构造成损伤, 包括颌下腺、甲状腺等腺体, 导致如口干、吞咽困难、甲状腺功能障碍等一系列放疗副反应。随着磁共振成像(magnetic resonance imaging, MRI)和调强放疗技术的进步, 阳性淋巴结的检出率和局部控制率已得到大幅提高, 此时, 基于风险分层对颈部淋巴结区域进行更为精准的放疗覆盖变得更加重要。大量回顾性证据表明, 鼻咽癌患者的区域淋巴结转移通常以自上颈向下有序的模式进展——以咽后淋巴结和II区淋巴结为转移第一站, 继而向III区和Va区淋巴结进展[100-102]。因此, 对低危淋巴结区域的预防性放疗进行豁免是减少毒性而保证疗效的可行手段。

3.4.1 内侧组咽后淋巴结的选择性照射 咽后淋巴结(retropharyngeal lymph node, RLN)可分为内侧组和外侧组两组, 是鼻咽癌淋巴引流的第一站。常规治疗推荐对内侧组及外侧组咽后淋巴结进行全覆盖放疗[50]。然而, 由于内侧组咽后淋巴结毗邻咽缩肌, 对其照射将不可避免地累及此肌, 引起迟发性吞咽困难、隐匿性误吸及与吞咽相关的误吸性肺炎等并发症[103-105]。

针对鼻咽癌区域淋巴结转移规律的研究表明, 内侧组咽后淋巴结受累率极低(0%~0.3%)[70,106], 提示常规针对内侧组咽后淋巴结进行的预防性照射可能并非必要。一项回顾性病例对照研究比较了进行和未进行内侧组咽后淋巴结预防性照射患者的疗效, 结果显示, 两组患者在5年局部无复发生存率、区域无复发生存率、无远处转移生存率及总生存率方面均无显著差异[107]。此外, 未进行内侧组咽后淋巴结照射患者的3级急性口腔黏膜炎发生率显著降低。2023年, 一项纳入568例鼻咽癌患者的非劣效性、随机、III期临床试验进一步证实了这一结果[98](表2)。意向性治疗分析结果显示, 未进行内侧组咽后淋巴结照射组与照射组在3年局部无复发生存率方面无显著差异(95.3% *vs* 95.5%, P=0.95)。此外, 两组的3年总生存率、远处无复发生存率及区域无复发生存率也无显著差异。同时, 未照射组的1级及以上急性和迟发性吞咽困难发生率明显降低。患者报告的结果表明, 未照射组患者的整体健康状况、角色及社会功能、疲劳感及吞咽能力均优于照射组。这些研究结果为豁免内侧组咽后淋巴结预防性照射提供了有力的支持。

3.4.2 Ib区淋巴结的选择性照射 颌下腺位于Ib区内, 对该区域进行照射可能增加患者放疗后口干的风险[108]。对鼻咽癌区域淋巴结转移规律的研究表明, Ib区淋巴结受累率极低, 且区域淋巴结少见跳跃性转移[100,102], 提示在预防性照射中豁免Ib区淋巴结可能是可行的。ZHANG等[109]研究发现, 初诊时Ib区淋巴结转移的高危因素包括: IIa区淋巴结具有包膜外侵犯、IIa区淋巴结最大径≥2 cm、口咽部受累或存在双侧颈部淋巴结转移。在该研究中, 904例不满足上述标准的低危患者未常规进行Ib区淋巴结照

表2 近期主要评估减毒化疗方案及缩小放疗靶区在鼻咽癌中治疗应用的III期临床试验

Table 2 Recent main phase III trials evaluating low-toxicity chemotherapeutic options and reduced radiation field for NPC management

研究 Study	实验组治疗 Experimental treatment	对照组治疗 Control treatment	主要纳入标准 Major inclusion criteria	样本量 Sample size	主要终点 Primary endpoint (experimental *vs* control; difference [95% CI]; *P* for noninferiority)	临床意义和减毒效果 Clinical significance and toxicity reduction (experimental *vs* control; difference [95% CI])
TANG et al[95] 2018 TANG et al[96] 2021	Nedaplatin 100 mg/m² q3wks × 3 concurrently with IMRT	Cisplatin 100 mg/m² q3wks × 3 concurrently with IMRT	Stage II-IVB NPC (T1-4N1-3 or T3-4N0)	402	5-year PFS: 79.8% *vs* 81.4%; –1.6% (–9.5% to 6.3%); *P*=0.002 0	Suggested nedaplatin as a low-toxicity, equivalent alternative to cisplatin in CCT Significantly lower incidence of any grade or grade 3-4 auditory toxic effects (grade 1: 41.0% *vs* 56.6%, *P*=0.002; grade 3-4: 10.5% *vs* 17.7%, *P*=0.04)
LÜ et al[97] 2021	IC: lobaplatin 30 mg/m² d1, fluorouracil 800 mg/m² d1-5, q3wks × 2; CCT: lobaplatin 30 mg/m², q3wks × 2 with IMRT	IC: cisplatin 100 mg/m² d1, fluorouracil 800 mg/m² d1-5, q3wks × 2; CCT: cisplatin 100 mg/m², q3wks × 2 with IMRT	Stage III-IVB NPC	502	5-year PFS: 75.0% *vs* 75.5%; 0.5% (95% CI –7.1 to 8.1; *P*=0.007 0) (ITT)	Suggested lobaplatin as an equivalent low-toxicity alternative to cisplatin in IC and CCT Significantly lower frequency of grade 1-2 nephrotoxicity (21% *vs* 37%, *P*<0.000 1), weight loss (32% *vs* 66%, *P*<0.000 1), grade 3-4 neutropenia (*P*<0.000 1), leucopenia (*P*=0.045 0), anemia (*P*<0.000 1), nausea (*P*<0.000 1), and vomiting (*P*<0.000 1)
TANG et al[66] 2022	IMRT	IMRT with concurrent cisplatin 100 mg/m² q3wks × 3	Stage II/T3N0M0 NPC with all <3 cm nodes, no level IV/Vb nodes; no ENE; EBV- DNA <4 000 copies/mL	341	3-year FFS: 90.5% *vs* 91.9%; –1.4% (1-sided 95% CI, –7.4% to ∞); *P*<0.001 0	Validated safe exemption of chemotherapy in IMRT-treated low-risk stage II/T3N0M0 NPC Significantly lower incidence of grade 3-4 adverse events (17% *vs* 46%; −29% [−39% to −20%]) and higher quality of life scores with IMRT alone
TANG et al[65] 2022	Elective ipsilateral upper neck irradiation sparing the uninvolved lower neck	Standard whole-neck irradiation	N0-1, nonmetastatic NPC	446	3-year RRFS: 97.7% *vs* 96.3%; –1.4% (95% CI –4.6 to 1.8); *P*<0.000 1	Validated safe exemption of lower neck prophylactic irradiation in N0-N1 disease Lower incidence of late toxicity: any grade of hypothyroidism (30% *vs* 39%), skin toxicity (14% *vs* 25%), dysphagia (17% *vs* 32%), and neck tissue damage (23% *vs* 40%) in the UNI group
MAO et al[98] 2023	MRLN-sparing radiotherapy	MRLN-involving radiotherapy	Newly diagnosed, nondistant metastatic NPC without MRLN involvement	568	3-year LRFS: 95.3% *vs* 95.5%; –0.2% (1-sided 97.5% CI –3.6 to ∞); *P*<0.001 0	Validated safe exemption of MRLN prophylactic irradiation Significantly lower incidence of grade ≥1 acute dysphagia (25.5% *vs* 35.1%, *P*=0.01) and late dysphagia (24.0% *vs* 34.3%, *P*=0.008); patient-reported outcomes: global health status (−5.6 [−9.1 to −2.0], *P*=0.002), role functioning (−5.5 [−7.4 to −3.6], *P*<0.001), social functioning (−6.2 [−8.9 to −3.6], *P*<0.001), fatigue (7.9 [4.0–11.8], *P*<0.001), and swallowing (11.0 [8.4 to 13.6], *P*<0.001) in the MRLN-sparing group

NPC: 鼻咽癌; CI: 置信区间; IC: 诱导化疗; CCT: 同期化疗; IMRT: 调强放疗; q3wks: 每3周; PFS: 无进展生存率; ITT: 意向性治疗; d1: 第1天; EBV: EB病毒; ENE: 包膜外侵犯; FFS: 无失败生存率; UNI: 上颈部照射; RRFS: 区域无复发生存率; LRFS: 局部无复发生存率; MRLN: 内侧组咽后淋巴结。

NPC: nasopharyngeal carcinoma; CI: confidence interval; IC: induction chemotherapy; CCT: concurrent chemotherapy; IMRT: intensity-modulated radiation therapy; q3wks: every three weeks; PFS: progression-free survival; ITT: intention-to-treat; d1: day 1; EBV: Epstein-Barr virus; ENE: extranodal extension; FFS: failure-free survival; UNI: upper neck irradiation; RRFS: regional relapse-free survival; LRFS: local relapse-free survival; MRLN: medial retropharyngeal lymph node.

射, 在3年随访期内, 无一例患者在该区域出现复发。OU等[110]的研究也得出了类似结果。基于这些发现, 国际临床靶区勾画指南(the international guidelines for the delineation of clinical target volumes)将上述危险因素纳入了Ib区淋巴结照射的推荐标准[111]。当前推荐的Ib区照射标准包括: Ib区淋巴结受累、颌下腺受累、口腔及鼻腔前部受累、II区淋巴结具有包膜外侵犯或II区淋巴结最大径超过2 cm。

然而, 近期两项回顾性研究发现, 对于具有上述II区淋巴结高危因素的患者, 豁免Ib区淋巴结照射仍能取得较高的5年区域无复发生存率, 且其与接受Ib区照射的患者相比无显著差异[108,112]。此外, 照射组患者5年后发生1级及以上口干的概率显著增高[108]。这些研究结果表明, 将Ib区淋巴结豁免照射标准扩展至具有当前II区淋巴结高危因素的患者可能是安全的。然而, 仍需高质量的前瞻性研究提供更高级别的证据。

3.4.3 选择性上半颈照射 鼻咽癌颈部淋巴结转移的侧向性研究显示, 当患者为单侧上颈部淋巴结转移时, 对侧中颈或下颈部淋巴结转移的发生率低于2%[100,102], 而当双侧上颈部淋巴结均出现转移时, 中颈或下颈部淋巴结的转移率显著增加[102]。基于此规律, LI等[102]提出了以下预防性颈部照射方案: 对N0(无淋巴结转移)患者, CTV2应覆盖双侧上、中颈部(包括RLN以及II、III和Va区淋巴结); 对单侧颈部淋巴结转移的患者, CTV2应覆盖受累侧全颈及对侧上、中颈部; 对双侧颈部淋巴结转移的患者, CTV2则应包含双侧全颈。

TANG等[65]进一步通过一项非劣效性、随机、III期临床试验验证了该推荐方案(表2)。该试验比较了对N0~1期患者进行常规标准全颈照射和选择性单侧上颈照射的局部区域控制率, 其中, 选择性单侧上颈照射范围包含受累侧全颈和非受累侧上颈(II、III和Va区淋巴结), 而不对下颈部区域(IV区和Vb区淋巴结)进行预防性照射。结果显示, 二组的3年区域无复发生存率相当(分别为97.7%和96.3%; 非劣效性P<0.000 1)。此外, 尽管两组在急性放射性毒性反应发生率方面类似, 但选择性单侧上颈照射组的晚期毒性, 包括任何级别的甲状腺功能减退、皮肤反应、吞咽困难及颈部组织损伤均更少。

该研究为N0~1期患者豁免无转移侧下颈部预防性照射提供了一级证据。这一放疗范围不仅在维持区域控制率的基础上减少了治疗毒性, 同时也保留了能够产生肿瘤杀伤性免疫细胞的淋巴结功能, 这些细胞可参与抗肿瘤免疫反应, 可能有助于提高免疫检查点抑制剂的疗效[113]。

除了对鼻咽癌患者的淋巴引流区域进行选择性预防照射外, 近来的减毒研究还聚焦于基于诱导化疗敏感性进行个体化放疗。两项II期临床试验探讨了对于在诱导化疗后达到完全缓解或部分缓解的儿童及成人鼻咽癌患者, 使用60 Gy的调强放疗联合同期顺铂化疗的疗效, 其3年及2年无进展生存率分别为91%和94.8%[114-115]。口干为主要的晚期毒性反应, 两项研究均未观察到其他严重的不良反应。当前有三项随机对照试验正在II~III期鼻咽癌患者中进一步探究基于诱导化疗或放疗敏感性的减剂量放疗相比于常规放疗的疗效(分别为60或63.6 Gy/30次分割 *vs* 70 Gy/33次分割; NCT04448522、NCT05304468和NCT06239727), 其研究结果有望进一步优化鼻咽癌的个体化治疗。

4 疗效再提升: 鼻咽癌免疫治疗新进展

鼻咽癌组织具有独特的免疫学特征, 包括密集的免疫细胞浸润[52]、免疫抑制微环境[116]以及程序性死亡配体-1(programmed cell death-ligand-1, PD-L1)的高水平表达[117]。这些特征凸显了免疫检查点抑制剂在鼻咽癌治疗中的增效潜力。

目前, 三项III期临床试验已证实, PD-1抑制剂联合GP化疗作为复发或转移性鼻咽癌患者的一线治疗可显著延长无进展生存期[118-120]。对于局部晚期鼻咽癌, PD-1抑制剂结合放化疗是否能进一步增效是近期研究的热点。多项II期临床试验报道了在诱导化疗、辅助化疗、诱导及辅助化疗或全程治疗期间加入PD-1抑制剂或PD-L1抑制剂的疗效[121-124]。客观缓解率为88.9%~94.4%, 2年无进展生存率为69.6%~91.8%, 显示出免疫治疗的可观前景。目前唯一已发表的探索PD-1抑制剂在局部晚期鼻咽癌中疗效的大规模III期临床试验表明, 对于高危局部晚期危鼻咽癌患者, 在GP诱导化疗、同期放化疗及辅助治疗过程中增加信迪利单抗治疗可将患者的复发或死亡风险降低41%, 并使3年无事件生存率提高10%(86.1% *vs* 76.0%; HR 0.59, 95% CI 0.38-0.92; P=0.019)[125]。此外, 信迪利单抗组相比于标准治疗组的远处转移和局部区域复发风险均显著

降低(3年无远处转移生存率: 90.3% *vs* 82.8%, HR 0.57 [95% CI 0.33-0.98], *P*=0.039; 3年无局部复发生存率: 93.4% *vs* 86.8%, HR 0.52 [95% CI 0.27-0.97], *P*=0.038)。值得注意的是, 两组患者在生活质量方面无显著差异。该研究结果提示, PD-1抑制剂联合放化疗可能取代单纯放化疗成为高危局部晚期鼻咽癌的治疗新标准。目前, 多项临床试验正在评估在鼻咽癌诱导或辅助治疗阶段加入免疫检查点抑制剂的疗效和安全性, 或作为传统化疗替代方案的可行性。其结果有望进一步优化免疫治疗与放化疗联合应用的时机与方案, 为鼻咽癌治疗带来新的启示。

5 结论

近年来, 鼻咽癌治疗研究主要集中于将化疗与放疗相结合以进一步提高疗效。诱导化疗联合同期放化疗已成为局部晚期鼻咽癌的首选治疗模式, 其中, TPF和GP方案在国际指南中被推荐为诱导化疗的首选方案。对于高危患者, 节拍辅助化疗是一种有效且耐受性良好的维持策略, 可在延长患者生存期的同时维持生活质量。在减毒方面, 更为精准的分期带来了更准确的预后预测, 并更有效地指导了分层治疗。对于低危患者, 豁免同期化疗、选用低毒等效化疗药物或豁免低危区域预防性放疗等策略已显现出更低的治疗毒性, 同时保持了治疗效果, 使患者的生活质量提升。

此外, 免疫检查点抑制剂与放化疗相结合可实现局部晚期鼻咽癌治疗的进一步增效, 其与放化疗结合的最佳时机和方案是近期研究的热点。当前进展中的研究有望进一步促进鼻咽癌个体化治疗的发展, 在提升患者生存率的同时, 使患者的生活质量得到保证。

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