中国细胞生物学学报 Chinese Journal of Cell Biology 2025, 47(3): 717–729
DOI: 10.11844/cjcb.2025.03.0033
CSTR: 32200.14.cjcb.2025.03.0033

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复发/转移鼻咽癌精准防治研究进展

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摘要　鼻咽癌是侵袭性和转移率最高的头颈恶性肿瘤, 复发/转移是其治疗失败的主要原因。随访对于早期发现鼻咽癌复发/转移病灶意义重大, 在随访策略上不断精进有助于实现复发/转移鼻咽癌(recurrent/metastatic nasopharyngeal carcinoma, RM-NPC)的早诊早治。该文详述了鼻咽癌局部区域复发和远处转移各自不同的诊断手段。药物治疗方面, 免疫治疗、靶向治疗的发展以及联合治疗方案的不断优化使得不适宜局部治疗RM-NPC的治疗取得突破性进展。该文分别从一线、二线、三线系统治疗方面汇总了当前药物治疗的前沿进展。而在局部治疗方面, 放疗包括复发鼻咽癌和转移鼻咽癌的放疗, 手术包括鼻咽、颈部复发手术和咽后复发手术。局部治疗技术的进步以及与药物治疗的联合使得它们在RM-NPC中的应用更加广泛和有效。

关键词　复发/转移鼻咽癌; 随访; 药物治疗; 放射治疗; 手术治疗

Advance in Precision Prevention and Treatment of Recurrent/Metastatic Nasopharyngeal Carcinoma

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收稿日期: 2024-12-02　　接受日期: 2025-01-06
国家自然科学基金(批准号: 82230034)资助的课题
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Reveived: December 2, 2024　　Accepted: January 6, 2025
This work was supported by the National Natural Science Foundation of China (Grant No.82230034)
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Abstract NPC (nasopharyngeal carcinoma) is the head and neck malignant tumour with the highest invasiveness and metastasis rate, and recurrence/metastasis is the main reason for its treatment failure. Follow-up is significant for early detection of recurrent/metastatic lesions in NPC, and the continuous improvement in the follow-up strategy can help to achieve early diagnosis and treatment of RM-NPC (recurrent/metastatic nasopharyngeal carcinoma). This review details the different diagnostic tools for each of locoregional recurrence and distant metastasis of NPC. In terms of drug therapy, the development of immunotherapy, targeted therapy and the continuous optimisation of combination therapy have led to breakthroughs in the treatment of RM-NPC, which is not suitable for local treatment. This review summarises current advances at the forefront of drug therapy in terms of first-, second- and third-line systemic therapy, respectively. As for local therapy, radiotherapy includes radiotherapy for recurrent NPC and metastatic NPC, and surgery includes recurrent surgery of the nasopharynx and neck and recurrent surgery of the retropharynx. Advances in local therapy techniques and combination with drug therapy have made their application in RM-NPC more widespread and effective.

Keywords recurrent/metastatic nasopharyngeal carcinoma; follow-up; drug therapy; radiotherapy; surgery

鼻咽癌是来源于鼻咽上皮的恶性肿瘤，常见于咽隐窝。中国南方是世界上鼻咽癌发病率最高的地区之一，广东的肇庆、中山和广州是核心高发区，男性的年龄标准化发病率为22.2~27.2/10万，且好发于青壮年时期，容易对社会、经济、劳动力及家庭造成重大冲击[1]。放射治疗联合或不联合化疗是初治鼻咽癌的主要治疗方法，目前随着放疗技术的进步和广泛应用，初治非远处转移鼻咽癌5年总生存(overall survival, OS)率可达80%左右[2-4]。然而，鼻咽癌是一种特殊类型的头颈癌，无论在流行病学、病理学、临床表现或治疗反应等方面都不同于其他头颈部黏膜癌，是一种侵袭性和转移率最高的头颈恶性肿瘤，约10%的患者在初次就诊时即发生远处转移[5-6]，70%~80%的患者诊断为局部区域晚期鼻咽癌，治疗后复发/远处转移率也高达20%~30%[7]。因此，复发/转移仍是鼻咽癌治疗失败的主要原因。实现复发/转移鼻咽癌(recurrent/metastatic nasopharyngeal carcinoma, RM-NPC)的精准防治，已成为延长鼻咽癌患者生存期的研究热点和重点[-9]。

1 随访

鼻咽癌治疗后的随访对于早期发现复发/转移病灶十分重要。随访手段包括问诊、体格检查、外周血爱泼斯坦−巴尔病毒脱氧核糖核酸(Epstein-Barr virus deoxyribonucleic acid, EBV DNA)拷贝数检测、直接/间接鼻咽镜检查和影像学检查等。鼻咽癌的首次随访通常在治疗后12~16周进行，主要针对局部和全身病灶进行系统评估[10-11]。有研究提示，治疗后6~9个月内达到临床完全缓解(complete response, CR)的延迟，可能不会对患者的预后产生负面影响[12]，但这一观点并没有得到临床医生的广泛认可。

在鼻咽癌治疗后随访时间上，已有报道提示鼻咽癌调强放疗(intensity modulated radiotherapy, IMRT)后10年内复发/转移风险主要集中在前5年，其后风险显著下降[1-14]。且鼻咽癌患者治疗后5年内的主要死亡原因是肿瘤复发/转移，其他原因相对较少[15]。IMRT时代下，复发风险呈现两个高峰期：一个出现在治疗后的1.5年，涉及肿瘤−淋巴结−转移(tumor-node-metastasis, TNM)分期为T3、T4及N2、N3的患者；另一个高峰则在治疗后3.5年，涵盖TNM分期中所有T分期以及N2、N3的患者[16]。另有一项大数据研究详细描绘了7 043例鼻咽癌患者治疗后5年内复发风险的动态变化，并制定了一套平衡了随访效果和时间成本的策略，实现了肿瘤的个体化随访[17]。2024年中国临床肿瘤学会(Chinese Society of Clinical Oncology, CSCO)指南以及美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)指南都推荐将鼻咽癌的随访重点集中在治疗后的前5年。

在鼻咽癌随访手段方面，一项基于马尔可夫模型的经济效益分析结果显示，相比于常规的影像学随访，使用血浆EBV DNA载量指导下的影像学随访能够维持相似的检出率，同时减少了近3/4的非必要影像学检查，从而显著降低了患者的随访成本并节约了医疗资源[18]。值得关注的是，在随访阶段，患者血浆EBV DNA载量由零变为重新可测或持续上升往往提示疾病的复发/转移，且其上升时间可早于影

像学检测出病灶2~3个月, 并且这一指标提示远处转移方面的灵敏度显著高于其对局部区域复发的提示价值[19-21]。因此, 随访阶段的血浆EBV DNA是判断治疗失败的重要标志物, 展现出了巨大的临床价值, 尽管当前仍需更多的大型前瞻性研究来验证其效果, 并明确EBV DNA载量的最佳分界值。

在针对鼻咽癌局部区域复发的监测中, 目前的常用手段包括鼻咽电子内镜、外周血EBV DNA拷贝数检测和鼻咽及颈部磁共振成像(magnetic resonance imaging, MRI)等。鼻咽电子内镜能够清晰检测到鼻咽黏膜表面的复发病灶, 但它无法窥及黏膜下咽旁、颅底和颅内的病灶。约50%的局部区域复发患者出现外周血EBV DNA升高[21]。MRI在检测鼻咽黏膜以外的复发病灶时展现出较高的灵敏度和特异度, 是目前临床上常用的评估手段[22]。一项回顾性研究建议, 治疗后无症状的局部早期患者(TNM分期中的T分期为T1~2), 可以不常规进行MRI随访, 而局部晚期患者(TNM分期中的T分期为T3~4)则每年进行一次MRI随访[23]。虽然MRI和正电子发射计算机断层显像(positron emission tomography/computed tomography, PET/CT)在敏感性上相似, 但PET/CT在特异性方面更为突出, 因此更能有效区分放疗后变化与复发病灶[24]。然而, 由于PET/CT的成本较高, 普及率相对较低, 它并没有像MRI那样被广泛应用。

目前, 远处转移已成为鼻咽癌治疗失败的主要原因[4,25-26], 因此, 聚焦于远处转移的复查是治疗后患者随访的关键环节。远处转移的常用复查手段包括外周血EBV DNA拷贝数检测、胸腹部计算机断层扫描(computed tomography, CT)、全身骨显像和PET/CT等。其中, 外周血EBV DNA拷贝数检测操作简便, 且在诊断鼻咽癌远处转移方面表现出高诊断价值, 是一种有潜力的随访方法[19-21,27]。胸腹部CT和全身骨显像虽为随访中常用的检查手段, 但并非每个病人每次复查都常规使用, 其临床价值尚待进一步验证。PET/CT在诊断远处转移方面的特异性和灵敏性均较高, 但高昂的成本限制了其在鼻咽癌随访中的普及使用。

2 药物治疗

部分复发的鼻咽癌患者不适宜接受局部治疗, 对于这类患者及远处转移的患者, 主要的治疗策略是进行系统性药物治疗。表1和表2分别列举了RM-NPC药物治疗方面重要的随机对照和单臂临床研究, 揭示了随着免疫治疗、靶向治疗的发展以及联合治疗方案的不断优化, RM-NPC患者可有更多更好的治疗选择(图1)。

2.1 一线治疗

鼻咽癌标准一线治疗方案是吉西他滨联合顺铂(gemcitabine and cisplatin, GP), 该方案的制定基于临床试验NCT01528618(美国临床试验数据库的注册号)的研究结果[28-30]。这项试验是全球首个针对RM-NPC的III期临床试验, 也是首个明确显示OS获益的研究, 确立了GP方案在鼻咽癌一线治疗中的核心地位。随后, 多项研究探索了基于GP的一线联合治疗方案。其中最重要的是GP联合程序性细胞死亡蛋白1(programmed cell death protein-1, PD-1)单抗方案在提高无进展生存(progression-free survival, PFS)方面取得了显著进展。例如, JUPITER-02研究结果表明, GP联合特瑞普利单抗相比GP联合安慰剂, 可显著延长PFS[中位数, 11.7个月*vs* 8.0个月, 风险比(hazard ratio, HR)=0.52][31-32]。此外, CAPTAIN-1ST和RATIONALE-309研究也报道了GP联合其他PD-1单抗显著提高了PFS的结果[33-34]。基于以上研究, 我国国家药品监督管理局(National Medical Products Administration, NMPA)分别批准了GP联合特瑞普利单抗、GP联合卡瑞利珠单抗和GP联合替雷利珠单抗作为一线治疗RM-NPC的适应证。除此之外, 一项单臂II期研究探索了GP联合抗血管生成药物恩度一线治疗转移性鼻咽癌的疗效和安全性, 结果显示客观缓解率(objective response rate, ORR)为85.7%, 中位PFS为19.4个月[35]。一项回顾性研究发现GP联合抗表皮生长因子受体(epidermal growth factor receptor, EGFR)单抗一线治疗RM-NPC的ORR为67.9%, 中位PFS为10.3个月, 中位OS为42.8个月[36-37]。这表明GP联合抗血管生成或抗EGFR靶向药也可能在一线治疗RM-NPC方面展现出潜力。

铂类联合紫杉醇类药物也是一线化疗的常用选择, 尽管含铂三药方案在客观有效率和短期疗效上表现更佳, 但在总生存期方面并无显著获益[38-42]。一项I/II期研究显示, 白蛋白紫杉醇联合顺铂治疗RM-NPC具有较高的有效率, 同时具备可接受的安全性[43]。研究还发现白蛋白紫杉醇单周、双周及三周方案间的安全性与疗效无显著统计学差异。一项II期随机对照研究发现, 在一线紫杉醇联合卡铂

表1　复发/转移鼻咽癌系统治疗随机对照临床试验

Table 1　Randomised controlled clinical trial of systemic therapy for recurrent/metastatic nasopharyngeal carcinoma

临床试验 Clinical trials	关键入组标准 Key eligibility criteria	试验方案 Experimental regimen	对照方案 Control regimen	样本量 Sample size	客观缓解率 Objective response rate		中位总生存时间/月 Median overall survival /months		中位无进展生存时间/月 Median progression-free survival / months	
					试验组*vs*对照组 Experimental *vs* control	*P*值 *P* value	试验组*vs*对照组 Experimental *vs* control	HR (95% CI); *P*值 HR (95% CI); *P* value	试验组*vs*对照组 Experimental *vs* control	HR (95% CI); *P*值 HR (95% CI); *P* value
First line										
ZHANG et al (Phase III)[28]	Recurrent/metastatic disease; treatment-naive patient	Gemcitabine and cisplatin for 6 cycles	Fluorouracil and cisplatin for 6 cycles	362	64.0% *vs* 42.0%	*P*<0.000 1	29.1 *vs* 20.9	0·62 (0.45-0.84); *P*=0.002 5	7.0 *vs* 5.6	0·55 (0.44-0.68); *P*<0.000 1
MAI et al (Phase III)[31]	Recurrent/metastatic disease; treatment-naive patient	Toripalimab, gemcitabine and cisplatin for 6 cycles; toripalimab maintenance	Placebo, gemcitabine and cisplatin for 6 cycles; placebo maintenance	289	77.4% *vs* 66.4%	*P*=0.033 5	NR *vs* 33.7[32]	0.63 (0.45-0.89); *P*=0.008	11.7 *vs* 8.0	0·52 (0.36-0.74); *P*=0.000 3
YANG et al (Phase III)[33]	Recurrent/metastatic disease; treatment-naive patient	Camrelizumab, gemcitabine and cisplatin for 6 cycles; camrelizumab maintenance	Placebo, gemcitabine and cisplatin for 6 cycles; placebo maintenance	263	87.3% *vs* 80.6%	NR	NR *vs* 22.6	0.67 (0.41-1.11); NR	9.7 *vs* 6.9	0.54 (0.39-0.76); *P*=0.000 2
YANG et al (Phase III)[34]	Recurrent/metastatic disease; treatment-naive patient	Tislelizumab, gemcitabine and cisplatin for 6 cycles; tislelizumab maintenance	Placebo, gemcitabine and cisplatin for 6 cycles; placebo maintenance	263	69.5% *vs* 55.3%	NR	NR *vs* 23.0	NR	9.2 *vs* 7.4	0·52 (0.38-0.73); *P*<0.000 1
ZHOU et al (Phase II)[44]	Recurrent/metastatic disease; treatment-naive patient	Carboplatin, paclitaxel and bevacizumab for 6 cycles; bevacizumab maintenance	Carboplatin and paclitaxel for 6 cycles	86	87.2% *vs* 72.5%	*P*=0.105	21.0 *vs* 24.7	1.29 (0.78-2.12); *P*=0.326	7.5 *vs* 6.5	0·71 (0.44-1.13); *P*=0.148
LIU et al (Phase III)[45]	Newly diagnosed metastatic disease, achieved disease control after chemotherapy	Paclitaxel, cisplatin and capecitabine for 4-6 cycles; capecitabine maintenance	Paclitaxel, cisplatin and capecitabine for 4-6 cycles	104	25.0% *vs* 11.5%	NR	NR *vs* 41.5	0.59 (0.30-1.16); *P*=0.13	35.9 *vs* 8.2	0.44 (0.26-0.74); *P*=0.002
LIU et al (Phase III)[47]	Recurrent/metastatic disease; treatment-naive patient	Nab-paclitaxel, cisplatin and capecitabine for 6 cycles; capecitabine maintenance	Gemcitabine and cisplatin for 6 cycles	81	83.0% *vs* 63.0%	*P*=0.05	NR	NR	11.3 *vs* 7.7	0.43 (0.25-0.73); *P*=0.002
LU et al (Phase II)[46]	Metastatic disease; benefiting from the first-line treatment	Tegafur/gimeracil/oteracil maintenance	Follow up	204	NR	NR	33.6 *vs* 20.6	0.378 (0.260-0.548); *P*<0.001	16.9 *vs* 9.3	0.445 (0.327-0.634); *P*<0.001
Second line and above										
CHAN et al (Phase III)[56]	Platinum-pretreated and recurrent/metastatic disease	Pembrolizumab	Capecitabine/gemcitabine/docetaxel	233	21.4% *vs* 23.3%	NR	17.2 *vs* 15.3	0.90 (0.67-1.19); *P*=0.226 2	4.1 *vs* 5.5	1.28 (0.94-1.75); NR
EVEN et al (Phase III)[57]	Platinum refractory and recurrent/metastatic disease	Spartalizumab	Chemotherapy	122	17.1% *vs* 35.0%	NR	25.2 *vs* 15.5	NR; *P*=0.138	1.9 *vs* 6.6	1.36 (0.87-2.12); *P*=0.915

NR: 未报道; HR: 风险比; CI: 置信区间。

NR: not reported; HR: hazard ratio; CI: confidence interval.

表2 复发/转移鼻咽癌系统治疗单臂临床试验

Table 2 Single-arm clinical trial of systemic therapy for recurrent/metastatic nasopharyngeal carcinoma

临床试验 Clinical trials	关键入组标准 Key eligibility criteria	试验方案 Experimental regimen	样本量 Sample size	客观缓解率 Objective response rate	总生存 Overall survival		无进展生存 Progression-free survival	
					中位/月 Median /months	1年 1-year rate	中位/月 Median /months	1年 1-year rate
First line								
JIN et al (Phase II)[35]	Metastatic disease; treatment-naive patient	Gemcitabine, cisplatin and endostar for 4 cycles	30	85.7%	NR	90.2%	19.40	69.8%
HUANG et al (Phase I/II)[43]	Metastatic disease; failure or intolerance of standard treatment (up to one line), or ineligibility for standard therapy	Cisplatin and nab-paclitaxel for 4-6 cycles	80	66.0%	NR	NR	9.00	NR
YOU et al (Phase I)[49]	Recurrent/metastatic disease; treatment-naive patient	Gemcitabine, apatinib and toripalimab for 6 cycles; apatinib and toripalimab maintenance	41	90.2%	NR	95.0%	25.80	74.0%
ZOU et al (Phase II)[50]	Recurrent/metastatic disease; treatment-naive and ineligible for cisplatin-based therapy	Gemcitabine and toripalimab for 6 cycles; toripalimab maintenance	21	61.9%	NR	95.2%	11.80	46.8%
Second line and above								
LIM et al (Phase II)[58]	Recurrent/metastatic disease; EBV DNA$^+$; no more than one line of prior chemotherapy; not fit for platinum-based therapy	Nivolumab and ipilimumab	40	38.0%	19.5	NR	5.30	NR
TANG et al (Phase II)[59]	Recurrent/metastatic disease; failed at least first-line platinum-based chemotherapy	Apatinib and capecitabine	64	39.1%	15.7	65.6%	7.50	37.5%
DING et al (Phase II)[60]	Recurrent/metastatic disease; refractory to at least first-line systemic therapy; treatment-naive to immune checkpoint inhibitors	Camrelizumab and apatinib	58	65.5%	NR	NR	10.40	44.3%
YUAN et al (Phase II)[61]	Recurrent/metastatic disease; failed the first-line platinum-based chemotherapy	Camrelizumab and apatinib	40	65.0%	NR	82.5%	12.60	52.5%
	Recurrent/metastatic disease; failed PD-1 inhibitor	Camrelizumab and apatinib	32	34.3%	16.2	68.8%	4.50	18.8%
DING et al (Phase II)[62]	Recurrent/metastatic disease; failed at least one line of systemic platinum-containing chemotherapy and anti-PD-L1 immunotherapy (combined or sequential)	Camrelizumab and famitinib	18	33.3%	NR	87.7%	7.20	32.0%
LU et al (Phase II)[63]	Metastatic disease; failed platinum-based chemotherapy	Sintilimab and bevacizumab	33	54.5%	NR	NR	6.80	NR
CAI et al (Phase II)[64]	Recurrent/metastatic disease; failed the first-line platinum-based chemotherapy	Toripalimab and anlotinib	30	36.7%	NR	NR	9.50	NR
HAN et al (Phase IIa)[65]	Recurrent/metastatic disease; failed prior platinum and/or PD-L1 therapy	MRG003 (2.0 mg/kg)	30	39.3%	NR	NR	7.30	NR
		MRG003 (2.3 mg/kg)	31	55.2%	NR	NR	NR	NR
Third line and above								
YANG et al (Phase II)[55]	Recurrent/metastatic disease; failed at least two lines of chemotherapy	Camrelizumab	156	28.2%	17.4	NR	3.70	NR
CHEN et al (Phase II)[68]	Recurrent/metastatic disease; failed at least two lines of chemotherapy	Penpulimab	130	28.0%	22.8	66.1%	3.60	24.7%
SHI et al (Phase II)[69]	Recurrent/metastatic disease; failed at least two lines of chemotherapy	KL-A167	132	26.5%	16.2	60.5%	2.80	19.2%
CHEN et al (Phase II)[70]	Recurrent/metastatic disease; failed first-line platinum-based chemotherapy and second-line single agent or combined chemotherapy; immunotherapy-naive	Cadonilimab	23	26.1%	NR	79.7%	3.71	20.0%
FANG et al (Phase II)[71]	Recurrent/metastatic disease; failed at least two lines of chemotherapy	Anlotinib	39	20.5%	NR	58.3%	5.70	NR

NR: 未报道; PD-L1: 程序性细胞死亡-配体1; EBV DNA: 爱泼斯坦–巴尔病毒脱氧核糖核酸。

NR: not reported; PD-L1: programmed cell death-ligand 1; EBV DNA: Epstein-Barr virus deoxyribonucleic acid.

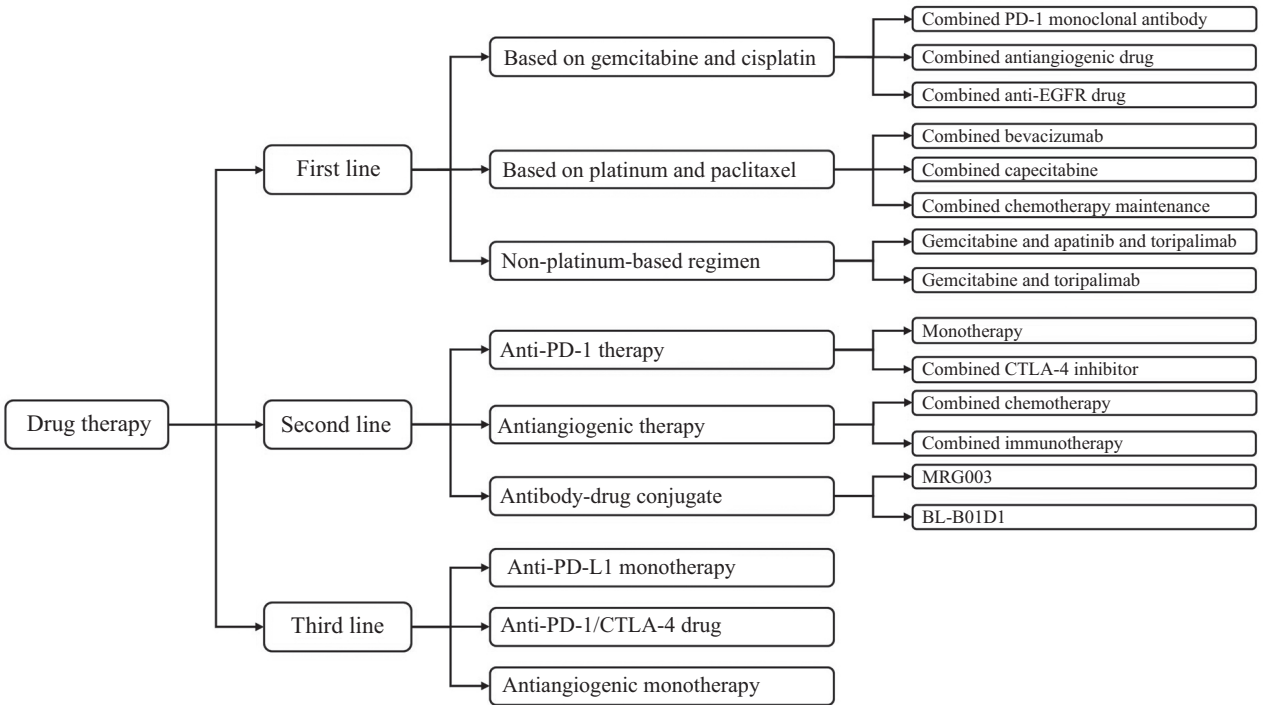

图1 复发/转移鼻咽癌药物治疗

Fig.1 Drug therapy for recurrent/metastatic nasopharyngeal carcinoma

的基础上, 增加贝伐珠单抗并不能延长PFS(中位数, 7.5个月*vs* 6.5个月, *P*=0.148)和OS(中位数, 21.0个月*vs* 24.7个月, *P*=0.326)[44]。在维持化疗方面, 一项小样本III期随机对照研究表明, 经过4~6个疗程的一线紫杉醇、顺铂和卡培他滨三药治疗并达到疾病控制的转移性鼻咽癌患者, 接受卡培他滨维持治疗的患者PFS显著优于未接受维持治疗的患者(中位数, 35.9个月*vs* 8.2个月, HR=0.44)。初步OS分析显示维持治疗组有更好的生存获益(中位数, 未达到 *vs* 41.5个月, HR=0.59)[45]。一项随机对照II期临床研究也发现, 一线化疗后替加氟/吉莫斯特/奥替拉西维持组在PFS和OS上均显著优于不维持组[46]。另外, 一项小样本随机对照研究表明, 在RM-NPC一线治疗中, 白蛋白紫杉醇联合顺铂和卡培他滨相比于吉西他滨联合顺铂, 能显著延长PFS(中位数, 11.3个月*vs* 7.7个月, *P*=0.002)[47]。然而, 一线诱导治疗后维持治疗的价值需要在免疫治疗背景下, 通过设计良好的大样本量III期临床研究进行进一步评估。

顺铂在一线治疗中仍处于主导地位, 然而, 其显著的毒副作用, 包括恶心、呕吐、严重的血液毒性、耳毒性和肾毒性, 显著降低了治疗的依从性和患者的生活质量[48]。因此, 有研究探索了一线去铂治疗的可能性。一项单臂研究结果显示“吉西他滨+阿帕替尼+特瑞普利单抗”三药联合方案在RM-NPC患者一线治疗中, ORR高达90.2%, 中位PFS为25.8个月, 23例(56.1%)患者出现≥3级治疗相关不良事件(treatment-related adverse events, TRAEs), 其中9例(21.9%)患者经历了≥3级的鼻咽坏死, 坏死的高危因素包括二程放疗和距离上次放疗不足12个月的间隔[49]。一小部分患者对顺铂不耐受, 无法接受多数铂类药物, 这通常见于同时患有肾损伤、心力衰竭、周围神经病、≥2级听力损伤等的患者。对此类患者一项样本较小的单臂研究发现, 吉西他滨联合特瑞普利单抗一线治疗RM-NPC的≥3级TRAEs发生率为23.8%, ORR为61.9%, 中位PFS为11.8个月[50]。

2.2 二线及以上治疗

对于一线含铂方案治疗失败的患者, 目前尚无强有力的挽救治疗方案, 目前鼓励患者参加设计严谨的临床试验。常规治疗策略包括采用一线未使用过的单药化疗, 如吉西他滨、多西他赛、卡培他滨等。同时, PD-1单抗在二线或多线治疗中也展现出一定的挽救治疗价值, 其单药有效率为20%~30%[37,51-55]。然而, 针对二线治疗, 虽然安全性上更有优势, 但是两项随机对照试验均未发现PD-1单抗单药相较于化疗能显著延长患者的生存时间。KEYNOTE-122研究发现, 帕博利珠单抗相比于化疗, OS并未得到显

著改善(中位数, 17.2个月*vs* 15.3个月, *P*=0.2262)[56]。另一项II期随机对照研究(NCT02605967)发现, PD-1单抗斯巴达珠单抗相比于化疗同样不能改善患者的PFS(中位数, 1.9个月*vs* 6.6个月, *P*=0.915)[57]。尽管如此, 对于无法耐受化疗或拒绝化疗的患者, PD-1单抗仍可作为一种治疗选择。另外, 一项针对爱泼斯坦−巴尔病毒(Epstein-Barr virus, EBV)阳性RM-NPC患者的单臂II期临床试验评估了纳武利尤单抗联合细胞毒性T淋巴细胞相关蛋白4(cytotoxic T lymphocyte-associated protein-4, CTLA-4)抑制剂伊匹木单抗治疗既往化疗失败患者的疗效, 研究的主要终点最佳总响应(best overall response, BOR)率虽未达到预设水平, 但仍可达到38%, 中位PFS和OS分别为5.3个月和19.5个月[58]。这项研究提示多靶点治疗或许可提高PD-1单抗的挽救治疗价值, 期待未来更多大样本随机对照研究的证实。

对于一线含铂化疗失败的患者, 抗血管生成药物展现出了一定的疗效。在抗血管生成药物联合化疗方面, 一项小样本II期单臂临床研究发现一线化疗失败的RM-NPC患者接受阿帕替尼联合卡培他滨治疗后, ORR为39.1%, 中位PFS为7.5个月, 中位OS为15.7个月, 36例(56.3%)患者出现了≥3级TRAEs[59]。鉴于阿帕替尼和卡培他滨的不良反应谱有重叠, 进一步研究该治疗方案的生存收益与安全性是必要的。在抗血管生成联合免疫治疗方面, 一项II期单臂研究发现, 卡瑞利珠单抗联合阿帕替尼治疗一线化疗失败RM-NPC患者的有效率为65.5%, 中位PFS为10.4个月[60]。值得注意的是, 这项研究纳入了近一半的仅局部区域复发的患者, 这可能部分解释了其PFS数据相较于历史数据的改善。在该研究中, 停用阿帕替尼最常见的原因是鼻咽坏死, 特别是在有鼻咽复发病灶或鼻咽再程放疗的患者中, 鼻咽坏死的风险显著增加。另一项II期临床试验评估了卡瑞利珠单抗联合阿帕替尼在铂类耐药(第一组, NCT04547088)和PD-1抑制剂耐药(第二组, NCT04548271)的RM-NPC患者中的安全性和疗效, 第一组的ORR为65%, 第二组为34.3%。47例(65.3%)患者出现了≥3级TRAEs[61]。此外, 一项小样本单臂研究探索了卡瑞利珠单抗联合法米替尼在既往程序性细胞死亡–配体1(programmed cell death-ligand1, PD-L1)单抗治疗失败的RM-NPC患者中的疗效及安全性, 结果显示ORR为33.3%, 中位PFS为7.2个月。8例(44.4%)患者出现了≥3级TRAEs, 4例患者出现≥3级鼻咽坏死, 2例患者出现≥3级鼻咽出血[62]。还有一项单臂II期研究探索性将信迪利单抗联合贝伐珠单抗用于治疗至少经一线化疗的RM-NPC患者, 结果显示ORR为54.5%, ≥3级鼻咽坏死发生率为9.1%[63]。另一项单臂II期研究评估了特瑞普利单抗联合安罗替尼二线及以上治疗RM-NPC患者(*n*=30)的疗效及安全性, 结果显示ORR为36.7%, 中位PFS为9.5个月, 最常见的≥3级TRAEs是黏膜炎(26.7%)和手足综合征(23.3%), 14名患者因TRAEs减少了安罗替尼的剂量[64]。这些结果提示对于鼻咽病灶残留或复发的RM-NPC患者, 抗血管生成药物应谨慎使用。

近年来, 针对多个靶点的抗体偶联药物(antibody-drug conjugate, ADC)开启了新的抗肿瘤治疗模式, ADC是一类通过连接子将细胞毒性药物连接到单克隆抗体的靶向生物制剂。MRG003是国内首个靶向EGFR的ADC, 一项IIa期临床研究探索性将MRG003运用在既往接受过含铂/PD-(L)1方案后进展的RM-NPC患者中, 设置两个剂量组(队列1剂量为2.0 mg/kg, 队列2为2.3 mg/kg)。结果显示队列1的ORR为39.3%, 中位PFS为7.3个月; 队列2的ORR为55.2%, 中位PFS尚不成熟。治疗相关严重不良事件的发生率为11.5%(7/61), 由于TRAEs的剂量减少率为13.1%(8/61), 停止治疗率为4.9%(3/61)。基于较高的ORR、潜在更优的疗效以及良好的耐受性, 相比于2.0 mg/kg, 2.3 mg/kg作为进一步研究的推荐剂量[65]。一项I/II期研究评估了MRG003与普特利单抗联合治疗EGFR阳性实体瘤患者的疗效和安全性, 在II期研究的9例EGFR阳性且一线PD-1单抗加铂类化疗进展的鼻咽癌患者中, ORR为77.8%, 有2例观察到CR, 5例部分缓解(partial response, PR), 2例疾病稳定(stable disease, SD)[66]。除此之外, 另一项I期研究探索了靶向EGFR×HER3(epidermal growth factor receptor 3)的双抗ADC药物BL-B01D1治疗局晚期或转移性实体瘤的安全性、耐受性和初步疗效, 其中二线及以上治疗RM-NPC患者中, ORR为37.8%, 中位PFS为6.8个月[67]。ADC药物目前仍处于早期探索阶段, 需要更多前瞻性随机对照研究证实其疗效及安全性。

2.3 三线及以上治疗

RM-NPC三线及以上治疗优选PD-1单抗单药, 这基于3项临床研究的结果。POLARIS-02研究中,

特瑞普利单抗治疗的ORR为23.9%, 中位PFS和OS分别为2个月和15.1个月[54]; CAPTAIN研究发现卡瑞利珠单抗治疗获得28.2%的ORR, 中位PFS和OS分别为3.7个月和17.4个月[55]; 另一项II期单臂研究发现派安普利单抗治疗的ORR可达28.0%, 中位PFS和OS分别为3.6个月和22.8个月[68]。基于以上研究, NMPA分别批准了特瑞普利单抗、卡瑞利珠单抗和派安普利单抗用于治疗既往接受过二线及以上系统治疗失败的RM-NPC患者。此外, 一项II期研究探索性将PD-L1单抗KL-A167用于既往至少二线治疗失败的RM-NPC患者, 结果显示ORR为26.5%, 中位PFS和OS分别为2.8个月和16.2个月[69]。双特异性抗PD-1/CTLA-4抗体卡度尼利单抗, 在二线治疗失败且未接受免疫治疗的RM-NPC患者中, ORR为26.1%, 展现出较好的潜力[70]。在抗血管生成药物方面, 一项单臂II期研究探索了安罗替尼单药治疗在多次治疗失败的RM-NPC患者中的疗效和安全性, 结果显示ORR为20.5%, 中位PFS为5.7个月[71]。

3 放射治疗

3.1 复发鼻咽癌的放疗

对于不适宜手术的复发鼻咽癌患者, 是否适合放疗与许多因素有关, 比如年龄、卡氏功能状态(karnofsky performance status, KPS)评分、复发分期以及大体肿瘤体积(gross tumor volume, GTV)[72-73], 甚至还包括复发时间间隔、复发部位、与邻近器官的关系、正常组织的耐受情况、既往放疗的不良反应情况以及之前原发灶的放疗剂量和对放化疗的敏感性等[74]。临床实际中需要综合考虑多方面因素决定是否行再程放疗。

对于再程放疗的剂量问题, 当处方剂量低于60 Gy(放疗剂量单位)时, 再程放疗无法实现良好的肿瘤局部控制; 而剂量高于70 Gy时, 再程放疗又显著增高了致死性并发症的风险。因此, 推荐再程放疗的剂量为(60~66) Gy/(27~33) F(fraction)[75-76]。在分割方式方面, 一项多中心随机对照研究对比了超分割IMRT和常规分割IMRT治疗复发鼻咽癌的效果, 发现了超分割IMRT相比于常规分割IMRT显著降低了患者的≥3级晚期毒性发生率(34% *vs* 57%, P=0.023), 同时, 超分割IMRT将3年OS率从55.0%提升至74.6% (HR=0.54, P=0.014)。这一研究证实了超分割IMRT可能是一种更有效且低毒的治疗方案, 为复发鼻咽癌的放疗策略提供了新的选择[77]。

关于再程放疗是否应联合化疗, 目前尚无明确结论; 而在再次放疗的基础上是否应结合免疫治疗, 根据一项单臂II期研究, 再程放疗联合免疫治疗显示出良好的肿瘤局控及较好的安全性, 但是否能转换为患者的长期生存获益, 尚需进一步的大样本随机对照研究来证实[78]。质子和重离子放疗在国内起步较晚, 它相比IMRT可以保证肿瘤部位高剂量的同时更好地保护周围正常组织, 小样本的回顾性研究已提示质子和重离子放疗在复发鼻咽癌中具有重要的应用潜力, 但目前仍缺乏随机对照研究的进一步证实[6]。

3.2 转移鼻咽癌的放疗

对于一线化疗反应良好的患者, 局部区域放疗(locoregional radiotherapy, LRRT)可能有助于改善初治转移鼻咽癌患者的预后。一项III期随机对照研究探索了在初治转移鼻咽癌患者一线化疗后加入LRRT的疗效和安全性[79], 结果显示, 放疗联合化疗组相对于单纯化疗组显著延长了患者的2年总生存率(76.4% *vs* 54.5%, HR=0.42, P=0.004)及无进展生存率(35.0% *vs* 3.6%, HR=0.36), 且局部放疗并未显著增加患者的毒副作用。该研究为局部放疗在初治转移鼻咽癌中的应用奠定了重要基础。然而, 在GP联合PD-1单抗的标准一线化疗时代, 局部放疗的重要性还需通过额外的III期随机对照研究进行验证。至于能否将免疫治疗联合放化疗用于初治转移鼻咽癌患者, 一项回顾性研究表明, 在初治转移鼻咽癌中, 姑息性化疗联合免疫治疗后序贯局部区域放疗可显著提高PFS[80]。此外, 一项单臂II期临床试验探索了一线化疗序贯放疗及特瑞普利单抗用于治疗初治转移鼻咽癌的疗效及安全性, 结果显示ORR为81.8%, 3年PFS率为44.9%[81]。

立体定向全身放射治疗(stereotactic body radiation therapy, SBRT)是鼻咽癌远处转移灶的一种局部治疗选择, 但其临床价值仍有待探索。一项II期随机对照研究(NCT04830267)探索发现, 卡瑞利珠单抗联合转移灶SBRT相比于单纯卡瑞利珠单抗不能显著改善转移鼻咽癌患者的ORR、PFS和OS[82]。而另一项单臂II期研究将SBRT与全身治疗结合用于一线治疗寡转移鼻咽癌患者, 结果发现1年的PFS和OS率分别为62%和87%, 且44个SBRT病灶中仅1处出现治疗失败, 未观察到与SBRT相关的≥3级TRAEs[83]。

但此研究需要更长时间的随访以评估肿瘤的长期预后。此外, 一项回顾性研究发现对初治转移鼻咽癌患者进行原发部位和转移灶放疗联合姑息化疗可提供OS获益, 提示其潜在的临床益处[84]。未来需要更多的前瞻性临床试验来进一步证实这一点。

4 手术治疗

4.1 鼻咽、颈部复发手术

复发鼻咽癌原发灶可手术切除的范围要求是肿瘤局限于鼻咽腔、鼻腔或者/和口咽腔内, 或伴有轻度咽旁侵犯, 但肿瘤边缘距颈内动脉≥0.5 cm, 或鼻咽肿瘤侵犯蝶骨基底部且范围较局限, 未达蝶窦侧壁和海绵窦; 相对适应症则是肿瘤超出此范围, 但根据各中心技术水平和综合条件可实施肿瘤根治性切除。

对于适宜手术的鼻咽复发灶或颈部淋巴结复发灶, 首选手术治疗。对于鼻咽复发灶, 推荐行经鼻内镜鼻咽肿物切除术。对于颈淋巴结复发灶, 推荐颈部淋巴结清扫术。鼻内镜微创手术在治疗可手术切除的复发鼻咽癌中, 兼具根治和微创的特性。一项回顾性病例配对研究发现, 对于可手术切除的复发鼻咽癌, 与传统再程放疗相比, 接受鼻内镜微创外科治疗的复发鼻咽癌患者5年OS率显著提高(77.1% *vs* 55.5%), 严重并发症发生率下降52.8%, 医疗费用下降约80%, 接受外科治疗的患者拥有更好的生存质量[85]。一项大型多中心随机对照研究对比了鼻内镜手术和IMRT治疗可手术切除复发鼻咽癌的疗效及安全性, 结果显示手术组3年OS率显著优于放疗组(85.8% *vs* 68.0%, HR=0.47, P=0.0015), 且≥3级放疗相关并发症发生率更低(13% *vs* 37%)[86]。此外, 一项回顾性研究表明, 针对可手术切除的复发鼻咽癌, 经鼻内镜低温等离子肿物切除术作为一种安全、有效且操作简便的方法, 显著降低了手术难度, 具有较强的推广性[87]。期待未来的研究进一步验证其疗效及安全性。

4.2 咽后复发手术

咽后淋巴结位于咽旁间隙, 位置深在、紧邻颈内动脉和后组颅神经。咽后淋巴结复发采用再程放疗, 副反应大, 治疗效果欠佳。手术治疗咽后淋巴结复发具有挑战性, 目前相关研究也较少。一项回顾性研究对单纯咽后淋巴结复发患者, 经内镜下经颌下咽旁入路进行咽后淋巴结清扫术, 手术的平均时间、出血量和术后住院时间分别为347.9 min、107.7 mL和8.7天[88]。所有患者2年无局部复发生存(local recurrence-free survival, LRFS)率、无远处转移生存(distant metastasis-free survival, DMFS)率、PFS率和OS率分别为63.9%、95.2%、59.9%和83.3%。晚期并发症包括吞咽问题、永久性置营养管、舌萎缩和肩部问题的发病率分别为19.4%(6/31)、9.7%(3/31)、9.7%(3/31)和9.7%(3/31)。经口机器人咽后淋巴结清扫术可能是更为微创的术式。另有一项小样本回顾性研究表明, 将经口机器人咽后淋巴结清扫术用于咽后复发鼻咽癌患者, 所有手术切缘均为阴性, 经中位19个月随访, OS率达100%, 仅有1例(10%)患者出现颈部复发, 相关并发症较轻[89]。

5 总结与展望

鼻咽癌随访对于早期发现复发/转移病灶意义重大, 期待通过更先进的筛查技术和随访策略实现RM-NPC的早诊早治。鼻咽癌复发/转移的治疗在近年来有了显著的进展, 随着免疫治疗和靶向治疗的进步, 为患者提供了更多的药物治疗方案选择和更好的生活质量(图1); 得益于放疗和手术技术的进步以及与药物治疗的联合, 局部治疗在RM-NPC中的应用更加广泛和有效(图2)。然而, 这些治疗方法的应用需要考虑到患者的个体差异和肿瘤的具体特征, 因此在实际应用中需要制定个体化的治疗方案。

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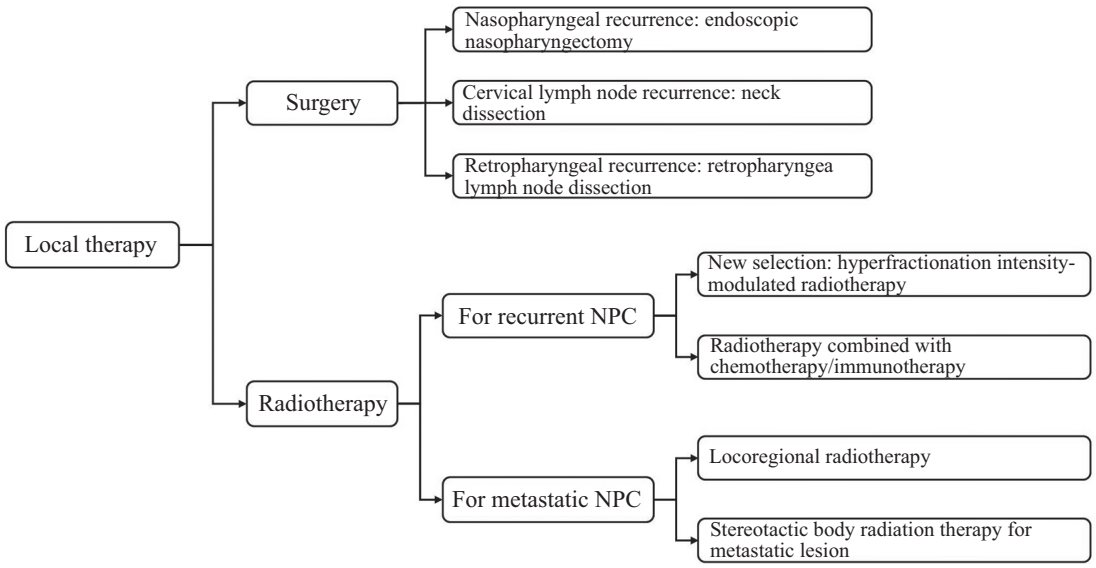

图2　复发/转移鼻咽癌局部治疗

Fig.2　Local therapy of recurrent/metastatic nasopharyngeal carcinoma

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