

局部晚期鼻咽癌的综合治疗进展

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摘要:鼻咽癌在流行病学、生物学行为及治疗方法上与其他肿瘤不尽相同,对放疗及化疗均具有较高的敏感性。放疗及化疗等手段结合的综合治疗已成为鼻咽癌的治疗标准。早期患者预后较好,但局部晚期鼻咽癌因其具有较高的局部复发率及远处转移率而导致治疗效果欠佳。如何提高其治疗效果仍在进一步临床研究中。

关键词:鼻咽癌;放射治疗;化疗;靶向治疗

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Progress of Combined Modality Therapy in Locally Advanced Nasopharyngeal Carcinoma

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ABSTRACT: There are many differences in epidemiology, biological behavior and treatment between nasopharyngeal carcinoma and other tumor. Nasopharyngeal carcinoma is highly responsive to both chemotherapy and radiotherapy. Radiotherapy combined with chemotherapy and other methods has become the standard treatment for nasopharyngeal carcinoma. Unlike early stage nasopharyngeal carcinoma, locally advanced nasopharyngeal carcinoma often has a poor prognosis because of higher local recurrence and distant metastases. How to improve the therapeutic effect is still under further clinical studies.

Key words: Nasopharyngeal carcinoma; Radiation therapy; Chemotherapy; Targeted therapy

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鼻咽癌(nasopharyngeal carcinoma, NPC)是我国最常见的恶性肿瘤之一。由于其生物学行为特殊,早期病变的症状和体征常不明显,约70%的患者确诊时已属于局部晚期鼻咽癌(locally advanced nasopharyngeal carcinoma, LA-NPC)^[1,2],即2010年版AJCC临床分期中的II期-B期。对于LA-NPC公认的治疗手段是以放射治疗为主、化疗为辅的综合治疗,一些临床研究结果表明LA-NPC治疗后5年总生存率(overall survival, OS)为50%~60%^[3,4],但其较高的复发率及远处转移率导致治疗效果不理想。近年来新兴的分子靶向治疗为LA-NPC的综合治疗提供了新的思路。现将近年来国内外LA-NPC的综合治疗进展综述如下。

1 放射治疗是LA-NPC的主要治疗手段

由于鼻咽深在的解剖位置、复杂的周围结构及特殊的肿瘤组织学类型,目前国内外肿瘤界公认放射治疗是NPC主要的根治手段。在过去的四十年,常规放疗及二维适形放疗是NPC放疗的主要方式^[3,5]。Chen等^[6]用常规放疗技术治疗556例LA-NPC,鼻咽部照射总剂量为66 Gy~80 Gy/6.5周~8周,颈部淋巴引流区照射总剂量为60 Gy~70 Gy/6周~7周,5年OS为66.41%。由于常规放疗中,患者的颞叶下部、颞颌关节、腮腺、颌下腺等器官和组织不可避免地受到较高剂量的照射,使患者放疗后容易出现严重的口干症、张口受限、放射性脑脊髓

损伤等毒副反应,严重影响患者的生活质量^[6]。

随着放射治疗新技术的开展,尤其是调强适形放射治疗(intensity modulated radiation therapy, IMRT)及图像引导放射治疗(image guided radiation therapy, IGRT)等新技术的临床应用,精确放疗在鼻咽癌治疗中的优势越来越凸显出来。目前一些研究已证实IMRT治疗NPC显示出了较高的肿瘤控制率和患者生存率、较低的放疗副反应^[7-9]。

与常规放疗相比,IMRT通过对肿瘤靶体积处方剂量进行设定,对肿瘤周围的重要组织及器官剂量进行限定,使用物理补偿器、多叶准直器静态及动态调强等技术实现对射线剂量强度的调节,并通过计算机逆向计划设计使射线剂量分布高度适合靶区形状^[10]。IMRT在保证肿瘤区足够照射剂量的同时,可更好地保护周围敏感器官,减少腮腺、颞颌关节、脑、脊髓等正常组织所受照射体积及剂量,减少口干症、张口受限、放射性脑脊髓损伤等一系列放射相关毒副反应的发生率^[11]。韩露等^[12]总结了305例接受IMRT的鼻咽癌患者的资料,其中II期168例,IIIa期92例。处方剂量为:肿瘤区(GTV)66.0 Gy~69.8 Gy,高危临床靶区(CTV-1)60 Gy~66.6 Gy,低危临床靶区(CTV-2)54.0 Gy~55.8 Gy,分割次数为30次~33次。结果提示II期、IIIa期患者的3年无病生存率(disease-free survival, DFS)分别为81.1%和71.8%。急性毒副反应包括照射野内皮肤反应(I度60.3%、II度35.1%、III度4.6%)、口腔黏膜反应(I度19.4%、II度51.1%、III度29.5%)。在晚期毒副反应中,IMRT治疗后3月I度、II度口干症的发生率分别为5%和95%;治疗后3年0度、I度及II度口干症分别为18.1%、78.4%及3.4%,未观

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观察到、度口干症。Chen等^[13]通过测量211例NPC患者IMRT治疗前后最大张口距离(maximal interincisal distance, MID)来观察患者放疗后张口受限的发生情况。所有患者治疗前的基础MID为45.5±5.5mm,治疗后6月、1年、2年、3年、4年、5年所测量值与基础MID相比的标准化MID分别为94.6%±9.9%、92.5%±10.5%、92%±10.6%、92.2%±10.5%、92.1%±10.2%、90.3%±11.4%。12名患者(5.7%)被确诊为~度张口受限,而未观察到~度的张口受限。作者认为IMRT技术能减少放疗后张口受限的发生率。Kam等^[14]比较了56例NPC患者IMRT与常规放疗对腮腺功能的影响。作者随机地将56例患者平均分入IMRT组及普通放疗组,IMRT组可观察到的严重口干症发生率明显低于普通放疗组(9.3%VS82.1%, $P=0.01$)。

目前多数学者认为^[9,10,12]应用IMRT治疗LA-NPC,在获得较高局控率及生存率的同时,可明显地减少放疗毒副反应的发生率,提高患者的生活质量。

2 化疗在LA-NPC治疗中的作用

LA-NPC治疗失败的主要原因常为远处转移及局部复发,其中远处转移更为常见^[15]。目前较多学者^[16-19]主张对LA-NPC患者应用同步放化疗(concurrent chemoradiotherapy, CCRT),即在放疗的同时进行化疗。CCRT治疗LA-NPC的疗效要优于单纯放疗或放疗加辅助化疗,可降低肿瘤局部复发率及远处转移率,提高生存率。

Chan等^[20]将350例~期NPC患者随机分为每周一次低剂量顺铂(40mg/m²/周)CCRT组和单纯放疗组。经中位随访时间为66个月随访后,CCRT组的OS较单纯放疗组高11%(70%VS59%, $P=0.065$)。国内外的荟萃分析证实了CCRT在LA-NPC治疗中的重要作用。Lanqendijk等^[21]总结了国外10项随机临床研究,包括2450例NPC患者。其中放疗配合化疗的患者(1226例)与单纯放疗的患者(1224例)相比,死亡危险比(HR)为0.82(95%CI:0.71~0.95, $P=0.01$)。作者进一步将这10项研究中以加入化疗的顺序分为三大类:新辅助化疗、同步放化疗及辅助化疗,分别与单纯放疗进行比较,发现CCRT的3年OS提高了20%,死亡HR为0.48(95%CI:0.32~0.72, $P=0.02$),作者认为CCRT对提高患者OS更有优势。Zhang等^[22]对7项随机研究进行了荟萃分析,结果发现在2年、3年及5年OS方面,CCRT与单纯放疗相比有较高的生存获益,其风险比(RR)分别为0.63(95%CI:0.50~0.80, $P=0.0002$)、0.76(95%CI:0.61~0.93, $P=0.010$)、0.74(95%CI:0.62~0.89, $P=0.001$)。Bajaj等^[23]所做的荟萃分析认为CCRT与单纯放疗比较5年OS提高了6%(62%VS56%),死亡HR为0.82(95%CI:0.71~0.94, $P=0.006$)。杨安奎等^[24]对国内18项关于CCRT与单纯放疗在LA-NPC中应用的比较研究进行荟萃分析。结果表明,CCRT组比单纯放疗组的3年、5年OS分别提高了12%(68.47%VS56.38%, $P<0.0001$)和11%(51.91%VS41.09%, $P<0.0001$),远处转移率减少了12%(26.19%VS38.71%, $P<0.0001$)。

CCRT可提高肿瘤治疗效果的作用机制可能为:(1)放射线及化疗药物直接杀灭原发肿瘤及微小转移灶;(2)CCRT后

使处于不同细胞周期的肿瘤细胞同步化,细胞阻滞于G2/M期,对放疗更敏感;(3)化疗药物通过抑制肿瘤细胞的亚致死性放射损伤的修复来增强放疗的作用,以达到协同增敏的目的;(4)CCRT避免了放射治疗时间的延迟^[11]。

CCRT在提高患者生存率的同时也增加了急性毒副反应发生率。Lin等^[9]的I期临床研究报道,284例患者随机分为两组,两组均采用相同的放疗方案。实验组在放疗的第1、5周分别予以顺铂20mg/m²/d及氟尿嘧啶400mg/m²/d,4天(96小时)持续静脉滴注,对照组仅行放射治疗。通过65个月的随访,结果显示CCRT组患者3年OS明显提高(72.3%VS54.2%, $P=0.0022$)。但CCRT组患者的急性毒副反应较单纯放疗组明显增加,以白细胞减少(0度36.9%VS60.8%、~度58.9%VS39.2%、~度4.3%VS0%, $P<0.05$)及呕吐(0度46.1%VS95.1%、~度49.6%VS4.9%、~度4.3%VS0%, $P<0.05$)尤为明显。

与单纯放疗相比,CCRT能提高LA-NPC患者的OS。但LA-NPC患者通过CCRT在获得较好治疗效果的同时,也会增加血液系统毒性、呕吐、口腔黏膜炎等并发症发生率的风险。

3 LA-NPC的分子靶向治疗

肿瘤分子靶向治疗(molecular targeted therapy)是近年来新兴的治疗手段。随着表皮生长因子受体(epidermal growth factor receptor, EGFR)及其信号传导机制的发现,EGFR的信号传导通路被认为与肿瘤细胞的增殖、转移和放射敏感性密切相关。目前EGFR拮抗剂主要有:EGFR单克隆抗体(如:西妥昔单抗、尼妥珠单抗等)及小分子酪氨酸激酶抑制剂(如:吉非替尼、索拉非尼等)。已有文献报道NPC高表达EGFR^[25],适合行抗EGFR的分子靶向治疗。

Bonner等^[26]将424例局部晚期头颈部癌患者随机分为西妥昔单抗联合放疗组(211例)及单纯放疗组(213例),结果发现联合组患者的中位生存时间较单纯放疗组长(49月VS29.3月,HR:0.74,95%CI:0.57~0.97, $P=0.03$),作者认为西妥昔单抗联合放疗可延长患者生存时间。Suntharalingam等^[27]报道43例LA-NPC患者接受西妥昔单抗联合TP方案化疗及放疗的I期临床研究。其中3年OS及3年DFS分别为59%及58%,3年局控率为72%。度以上的毒副反应发生率分别为:黏膜炎79%、皮疹9%、白细胞减少19%、放射性皮炎16%。有26%的患者因毒副反应太重而暂停放疗,作者认为西妥昔单抗联合化疗及放疗使急性毒副反应增加。Rodríguez等^[28]报道的一项关于尼妥珠单抗的实验研究,共纳入106例晚期头颈部鳞癌患者,分为实验组(尼妥珠单抗联合化放疗)及对照组(安慰剂联合化放疗)。结果表明,实验组较对照组有更多患者达到完全缓解(59.5%VS34.2%, $P=0.028$)。另外,一些吉非替尼、索拉非尼等药物的I期临床研究也提示分子靶向治疗在LA-NPC的综合治疗中有着较令人满意的疗效^[29,30]。

4 展望

精确放疗是LA-NPC的主要治疗手段。但LA-NPC单纯放疗疗效不佳,其主要原因为肿瘤远处转移及局部复发。放化疗综合治疗LA-NPC有助于提高肿瘤局控率及患者生存率目前

已逐步成为共识(1类证据),分子靶向治疗为提高LA-NPC的疗效提供了可能性。然而放疗联合分子靶向药物的综合治疗仍有许多需要解决的问题,如何改善放疗、化疗及分子靶向综合治疗增加患者皮肤、黏膜及血液系统的毒副反应是今后亟待研究解决的课题。

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