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THE 13TH ANNUAL MEETING OF CHINESE SOCIETY OF CLINICAL ONCOLOGY (CSCO) EDUCATIONAL BOOK

名誉主编 吴孟超 孙 燕
主 编 秦叔逵 马 军 游伟程
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中国临床肿瘤学进展 2010

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编 委 会

前　言

第十三届全国临床肿瘤学大会暨2010年CSCO学术年会定于2010年9月16日至9月19日在北京九华山庄隆重举行。本届大会由中国抗癌协会临床肿瘤学协作专业委员会(CSCO)、北京大学肿瘤医院和北京市希思科临床肿瘤学研究基金会联合主办，同时得到了《临床肿瘤学杂志》、《中国医学论坛报》、《医师报》、《中国处方药杂志》、24小时医学频道、丁香园网站以及万正医学网等专业媒体的支持协助。

本届年会将紧密围绕"关注分子靶标，优化治疗策略"的主题，保持鲜明的专业特色和学术风格，丰富充实会议内容，增加学术深度和广度，力求全面、准确地反映当前临床肿瘤学领域的新观念、新进展和新信息。组委会将重点突出原创性研究报告，特别举办抗癌新药临床研究、转化性研究和CSCO青年专家论坛等一系列专题论坛会。同时，特别邀请了一批国际、国内著名专家进行教育讲座，分享科研成果，交流实践经验。此外，本着发现和培养优秀人才的目的，本届大会将继续举办"成就未来——CSCO青年医师论坛星光大道"总决赛，为青年肿瘤学者提供交流思想、展示自我的平台。以期为广大会员和参会代表呈现一场高规格、高质量、高水平的学术盛会。

组委会共收到约稿150多篇和投稿1200多篇，内容涉及临床肿瘤学的多个领域和转化性研究，充分展示了我国在肿瘤规范化多学科综合治疗和个体化治疗方面的最新进展和最新成果，也展示了我国在肿瘤规范化多学科综合诊治和个体化治疗方面的长足进步。经大会学术委员会的认真审核和讨论，精选出121篇高水平的学术报告或讲座稿，整理和编辑成为《中国临床肿瘤学进展2010》正式出版发行，希望对广大与会代表了解国内外临床肿瘤学的现状和发展动态、实践规范化诊断治疗和积极开展临床研究有所帮助。

为了本书能够顺利出版，编委会各位专家不辞辛劳，认真撰写和审稿，付出了诸多心血；北京大学肿瘤医院、南京八一医院全军肿瘤中心、《临床肿瘤学杂志》编辑部、CSCO办公室的许多工作人员克服困难，加班加点，仔细审核校对，谨此一并致以最衷心的感谢！由于时间紧张，书中难免有错误和疏漏之处，敬请作者和读者不吝指正，并予谅解。

秦叔逵　马　军　游伟程

二〇一〇年八月十六日

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1 头颈部鳞癌的放化疗进展

中国医学科学院肿瘤医院　罗京伟　徐国镇　唐平章

头颈部鳞癌(squamous cell carcinoma of head neck,SCCHN)在全身肿瘤中所占的比例并不高,但因为头颈部解剖及功能的重要性,使得头颈部肿瘤的治疗需要综合考虑两方面的因素,一是尽可能地提高其局部区域控制率,另外一个是最大可能地保留患者的功能。

对早期的SCCHN,单一的治疗手段如手术或放疗已经获得了较为满意的疗效,没有必要加用化疗或其他治疗手段;而对于局部区域晚期的SCCHN,任何单一的治疗手段均不理想,采用传统的"手术+放疗"的综合治疗手段较单一的治疗手段局部区域控制率得到改善,但相当一部分是以牺牲患者的功能为代价,且总的生存也并不理想。因此为了进一步改善常规治疗手段对局部区域晚期SCCHN的疗效,并且最大可能地保留患者的功能,越来越多的局部晚期SCCHN现在采用以放疗、化疗、包括靶向治疗的非手术综合治疗手段。国外有关这方面做了大量的研究,主要体现在口咽、下咽、喉癌的临床治疗上。

以下根据近年来的文献,将放疗、化疗、靶向治疗在局部区域晚期SCCHN治疗中的作用给予简单概述。

一、放射治疗的进展

放射治疗如同手术,尽管属于局部治疗手段,但在SCCHN治疗中占有重要的地位:早期病变,放疗的效果基本类似于手术治疗;晚期病变,放疗+手术的综合治疗模式可以明显降低单一手术的局部区域复发率。

放疗技术的进步主要体现在:

1. 改变分割模式　在常规照射技术的前提下,通过改变分割次数可望进一步改善预后。如2000年RTOG报道的1113例晚期口腔、口咽、下咽、喉鳞癌病例,通过改变分割方式的随机性研究结果,显示1天2次的超分割技术和同步缩野加速超分割技术,较1天1次的常规分割照射技术改善了局部区域控制;2002年发表的荟萃分析结果,纳入1970~1998年的15个随机性研究、共6515例晚期SCCHN患者,通过改变分割方式,5年局控获益7%(46%→53%,$P<0.0001$),5年生存获益3%(36%→39%,$P=0.003$),其中尤以超分割照射技术获益最大,5年局部区域控制率或生存获益均为9%。结论为改变分割方式可以改善晚期SCCHN生存,其中尤以超分割为优。

2. 调强放疗技术的应用　常规放射治疗技术临床应用过程中,由于肿瘤邻近的正常器官和组织不可避免地包括在照射范围内,因此放疗常发生一定程度的并发症,如放疗过程中的急性皮肤、黏膜反应、吞咽困难、疼痛等,放疗后的晚期并发症如口干,咽下困难,龋齿,皮肤纤维化,感音性听力下降,骨、软骨结构的坏死等。这些并发症严重影响患者的生存质量。如何减少肿瘤周围正常组织的放疗受量,就成为减轻放疗并发症、改善生存质量的关键。

调强放射治疗作为放射治疗技术进展的一个里程碑式的标志,一经问世便应用于SCCHN放疗中。临床应用10年的实践表明,由于调强放疗采用多野照射技术,每个野中的子野强度可调,因此明显降低了肿瘤周围正常组织如腮腺、视神经、垂体、脑干、脊髓等的受量,放疗反应明显减轻,同时靶区内的剂量均匀度显著好于常规放疗。因此,调强照射技术用于SCCHN的放疗可望达到两个目的,一是降低并发症,改善生存质量;二是提高肿瘤的局部控制率。

临床三期研究已经明确,SCCHN采用调强放疗技术,放疗后口干的并发症明显减轻、患者生存质量明显改善。同时因为调强放射治疗较常规放疗治疗明显改善了靶区照射的剂量分布,因此也较常规放疗提高了局部控制率。但调强放疗是否改善了患者的总生存率目前尚无一致结论。

随着放疗设备的不断发展和更新,如图像引导直线加速器(IGRT)、断层治疗加速器(Tomotherapy)、旋转调强加速器(VMAT)临床中的应用,不仅可以解决摆位过程中的误差,保证治疗过程中的精确性和重复性,而且可以检测治疗过程中正常组织器官、肿瘤的动态变化,从而为进一步改善放疗在SCCHN治疗上的作用奠定了基础。

二、化疗的进展

化疗在局部区域晚期SCCHN中的应用主要分为诱导化疗、同步化疗和辅助化疗。有关SCCHN的文献荟萃分析自2000年发表以来,目前已更新两次。最新的资料已于2009发表,包括1965~2000年进行的87个随机性试验、共16 485

例 SCCHN 患者，结论同前两篇相似：5 年化疗的绝对获益率是 4.5%，单用诱导化疗受益有限，同步化疗受益明显，5 年绝对获益率是 6.5%，结论为同步化疗的获益显著大于诱导化疗。因此目前临床上对晚期头颈部鳞癌主张同步放化疗，而不提倡诱导化疗及辅助化疗。

1. 诱导化疗　诱导化疗自 20 世纪 80 年代曾经风靡一时，其代表性研究为美国退伍军人医院和 EORTC 24891 在喉/下咽癌中开展的相关研究，研究表明“DDP+5-FU”（PF）方案诱导化疗 2~3 个周期有效的患者，直接做根治性放疗，与根治性全喉切除术 + 术后放疗的疗效相同，但前者 2/3 的患者可通过放化疗保留喉的正常解剖功能。由于诱导化疗不能提高总生存（OS）率，而且这些研究都没有将单纯放疗作为对照组，同时随着 2000 年第一篇有关 SCCHN 放化疗荟萃分析结果，以及 2003 年 RTOG 91-11 临床研究结果的问世，均表明单纯诱导化疗对改善总生存无效，因此采用“DDP+5-FU”为标准方案的诱导化疗目前临床上的作用渐趋否定。

2. 同步化疗　RTOG91-11 的研究明确了诱导化疗 + 根治性放疗、同步放化疗、单纯放疗在晚期喉癌治疗中的作用：结果显示无论是局部区域控制率，还是喉保留率，都以同步放化疗组最好；同步放化疗 2 年喉保留成功率 88%，诱导化疗 + 放疗为 75%、单纯放疗喉保留率最低为 70%。诱导化疗 + 放疗与单纯放疗组间则无明显差异。因此临床上推荐同步放化疗的综合治疗方案。

三、手术 + 放疗 ± 同步化疗

根据肿瘤侵犯范围及其与周围重要组织的关系，局部晚期 SCCHN 一般分为可手术切除的病变与不可手术切除的病变。这两类病变的治疗策略有所不同，手术、放疗和化疗的结合方式及治疗地位亦有所区别。

1. 可手术切除的局部晚期 SCCHN 的治疗原则　对于可手术的局部晚期 SCCHN，一般以“手术 + 术后放疗”为标准治疗模式。术后放疗的指征包括切缘阳性、手术安全界不够（<5mm）、局部晚期肿瘤（$T_{3/4}$）、多个或多站淋巴结转移、淋巴结包膜外受侵、大血管/神经受累、骨/软骨或颈部软组织受侵及肿瘤细胞分化程度差等。

对于需要术后放疗的 SCCHN，尽管采用术后放疗较单一手术改善了局部区域控制率，但总的疗效仍不满意。因此此类病变在术后放疗的基础上加用化疗是否能进一步改善预后，就成为目前临床上需要解决的一个问题。

目前国外已经有随机性研究结果发表，如：

EORTC 22931 研究，将 334 例可手术的Ⅲ、Ⅳ期口腔、口咽、下咽\喉癌患者随机分为术后放疗和术后同步放化疗组，两组的照射技术、剂量相同（66Gy），同步化疗组为单药 DDP，100mg/m^2，在放疗的第 1、22、43 天用药，结果显示，术后同步放化疗组改善了单纯术后放疗的 3/5 年无瘤生存率（41/36% → 59/47%）、总生存率（49/40% → 65/53%）、5 年局部区域控制率（69% → 82%），但 3~4 级毒副作用明显增加（21% → 41%）。

RTOG 9501 研究，459 例可手术的口腔、口咽、下咽\喉癌患者，具备术后放疗指征如≥2 个淋巴结转移、淋巴结包膜受侵或切缘阳性者随机分为术后放疗和术后同步放化疗组，结果显示，术后同步放化疗组显著改善了单纯术后放疗的 2 年无瘤生存率（43% → 54%）、局部区域控制率（72% → 82%），对总的生存也有改善的趋势（57% → 63%），同时 3~4 级毒副作用明显增加（34% → 77%）。

分层分析发现，对于切缘阳性和淋巴结包膜外受侵的局部晚期 SCCHN 患者，术后同步放化疗获益作用明显，推荐为目前的标准治疗方案。

因此，对于手术切缘阳性和淋巴结包膜外受侵者，在术后放疗的基础上应考虑同步放化疗以进一步改善预后，而对于其他具有术后放疗指征的病例则无必要加用术后同步化疗。

2. 不可手术切除的局部晚期 SCCHN 的治疗原则　对于不可手术的局部晚期 SCCHN，放疗是重要的治疗手段。在化疗尚未在头颈部鳞癌得到广泛应用之前，主要是通过放疗技术的改变，如通过改变分割方式，改常规分割为超分割或后程补量加速分割模式来进一步改善预后。

目前随着化疗在临床中的拓宽应用，化疗也越来越多地介入到放疗中。由于“DDP+5-FU”方案的诱导化疗未能提高局部晚期 SCCHN 的生存率，而同步放化疗可提高生存率。因此不能手术的晚期 SCCHN 在放疗过程中同样主张同步化疗。

3. 含紫杉类方案（TPF）诱导化疗 + 同步放化疗方案在晚期 SCCHN 治疗中的作用　尽管同步放化疗作为晚期 SCCHN 的标准治疗模式，临床疗效有了一定的改善，但增加的幅度有限，因此目前仍有不少研究通过改变诱导方案，并合并同步化疗以进一步改善疗效。目前的临床研究多集中在原有标准诱导化疗方案“DDP+5-FU”的基础上加用含紫杉类方案（TPF）。

根据 EORTC 开展的系列研究（TAX323 和 TAX324）证实，对于不可手术切除的局部晚期 SCCHN，含紫杉类方案（TPF）诱导化疗 + 同步放化疗方案较同步放化疗的疗效有了进一步的改善。

TAX 323（EORTC 24971）研究了不能手术头颈部鳞癌病例，随机分为 TPF（n=177）和 PF 组（n=181），结果显示 TPF 组无进展生存期由 PF 组的 8.2 个月延长至 11 个月。中位随访 51.1 个月，中位生存时间由 PF 的 14.5 个月延长至 18.8 个月，延长了 4.3 个月（HR:0.73;P=0.02）。

TAX 324 试验比较了 DDP+5-FU（PF，n=246）和 PF 方案中加入 Taxotere（TPF，n=255）的疗效，至少随访 2 年，结果显示中位总生存期由 PF 方案的 30 个月延长至 71 个月（P=0.006），使肿瘤相关死亡的风险下降 30%，总的中位生存改善 30%。2010 年报道了其最少随访 5 年的远期效果：5 年时 TPF 组 52% 的患者存活，而 PF 组 42% 的患者存活。分层分析显示对于中位年龄超过 55 岁的患者，总生存 TPF 显著好于 PF（P=0.04），而年龄 <55 岁则无区别；而且下咽、喉癌肿瘤 TPF 组的 5 年无瘤生存显著改善（P=0.037）。值得注意的是 TPF 组口咽癌的总生存随着时间的延长获益作用增加，在 5 年时达到统计学差别（P=0.045，HR 0.69;95% CI 0.48~0.99）。两组气管切开和胃造瘘几率都不高。

同样，对于可手术的局部晚期 SCCHN，采用 TPF 诱导方案也获得了阳性的结果，如 Calais 于 2006 年报道了利用诱导化疗治疗可手术的局部区域晚期下咽、喉癌的结果，220 例随

机分为 108 例 PF 组(DDP 100mg/m^2 d_1,5-FU1000mg/m^2 d_{1-5}),112 例 TPF 组(T:75mg/m^2 d_1,DDP 75mg/m^2 d_1,5-FU 750mg/m^2 95% *CI* d_{1-5})。每 21 天一个周期,治疗有效的患者包括 CR\PR 者接受 70Gy 的根治性放疗,无效者全喉切除术 + 术后放疗。结果显示 TPF 组的治疗依从性良好,81.2% 患者完成原定方案治疗,而 PF 完成者 67.4%,总有效率(T and N)TPF 组 82.8%,而 PF 组 60.8%(P=0.0013);TPF 组 CR 率 60.6%、PF 组 46.7%;喉保留率 TPF 组 80%、PF 组 57.6%;血红蛋白浓度 >14g/L 和完成原定治疗方案 >80% 者对治疗的反应明显为好。中位随访 35 个月,3 年实际喉保留率 TPF 组 73%、PF 组 63%。结论为晚期喉、下咽癌,采用 TPF 方案的有效率明显好于 PF 方案、耐受性良好、保喉率高。

四、同步放化疗的并发症

尽管在多项研究中,同步放化疗都显示出优于单纯放疗或诱导化疗的优势。但是,我们也应清醒地看到,同步放化疗同时也增加了急性毒副反应的发生率:在 RTOG 9501 研究和 EORTC 22931 研究中,同步放化疗组与单纯放疗组的 3 级以上急性毒副反应发生率分别为 77% *vs* 34%(P<0.001)和 41% *vs* 21%(P=0.001)。而在 RTOG 91-11 研究中,同步放化疗组、单纯放疗组和诱导化疗组的 3 级以上急性毒副反应发生率分别为 80%、48% 和 68%。

过去多数研究都认为同步放化疗在增加急性毒副反应的同时,并不增加晚期毒副作用,但应注意这些研究发表时的临床观察时间较短,晚期损伤可能尚未完全显现出来。近年来越来越多的研究表明,同步放化疗可增加晚期毒副作用。如 2008 年发表的一篇研究,对 RTOG 91-11、97-03、99-14 研究中 230 例接受同步放化疗者的晚期毒副作用进行多项研究总结发现,严重毒副反应的总发生率为 43%,其中放疗后鼻饲管依赖时间 >2 年者占 13%,咽部功能严重异常者占 27%,喉部功能严重异常者占 12%,10% 的患者死于晚期毒副作用。

同时在应用化疗的过程中,因为毒副反应而患者不能耐受而不得不中断放疗的情况占有不少的比率,而中断放疗显著影响放疗效果也在一定程度上影响总体预后。

五、靶向治疗在晚期 SCCHN 治疗中的作用

由于内科化疗的介入,使得 SCCHN 的疗效有了一定程度的改善,但不可避免的毒副作用也妨碍了其在临床中的应用。目前在临床上积极寻找既能增加疗效,又不明显增加治疗毒副作用的有效治疗手段就变得日益重要。目前靶向治疗在临床中的应用,可望达到这个目的。

因为头颈部癌的 EGFR 表达率为 90%~100%。EGFR 的过度表达与无病生存降低,总生存降低,转移 / 侵袭风险增加。因此理论上讲如能阻断 EGFR 的表达,则可以明显改善 SCCHN 的预后。西妥昔单抗(C225),作为 EGFR 受体的阻断剂,在头颈部鳞癌的治疗上获得了较为理想的疗效。其中著名的为 Bonner 和 EXTREME 的随机性研究。

Bonner 研究于 2006 年发表在《新英格兰医学杂志》,为一多中心随机临床研究,研究入组病例 424 例,均为局部区域晚期 SCCHN,包括口咽、下咽、喉鳞癌。研究目的旨在比较单纯放疗和放疗联合 C225 在局部晚期 SCCHN 中的疗效。结果显示,根治性放疗在合并应用 C225 的基础上,使 2 年局部控制时间由单纯放疗的 14.9 个月延长至 24.4 个月(P=0.005),3 年总生存期由单纯放疗的 29.3 个月延长至 49.0 个月(P=0.03),3 年总生存率由 45% 提升至 55%;在疗效增加的同时,C225 除了自身的过敏反应及皮疹反应外,并不增加放疗的皮肤、黏膜及其他放疗副作用。该研究的随访 5 年结果已于今年发表,C225 治疗组 5 年总生存率 45.6%,而单纯放疗组仅 36.4%,表明在根治性放疗的基础上加用 C225,不仅放疗的并发症没有增加,而且 5 年绝对获益 9%。因此,局部区域晚期 SCCHN 的根治性放疗 +C225 治疗已写入 2009NCCN 治疗指南中,成为除同步放化疗外一种有效的治疗手段。

对复发或转移性头颈部鳞癌(R/M SCCHN),在一线化疗方案的基础上加用 C225 治疗,依然有效。根据 2007 年 ASCO 年会上报道的 C225 联合化疗一线治疗 R/M SCCHN 的Ⅲ期随机临床研究(EXTREME 研究)结果显示,与单用化疗组相比,C225 联合化疗组的中位生存期延长了 2.7 个月(P=0.036)。C225 并未改变铂类为主化疗的特征性副反应。这是在 R/M SCCHN 治疗领域中 25 年来首个生存获益超过铂类为主化疗的全身治疗方案。

总之,随着放疗技术的进步、内科化疗方案的完善、靶向治疗的应用,SCCHN 的预后较前有了一定的改善,但目前的依据主要是来自国外的材料,由于人种的差别、耐受性的不同,如何保证国人顺利完成放化疗综合治疗方案,并如何解决同步放化疗并发症的问题,以及拿出我们国人自己的确切临床研究结果,都是我们临床上不容忽视的事实,也是我们需要进一步研究探讨的问题。

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2 晚期鼻咽癌的系统性治疗进展
SYSTEMIC TREATMENT FOR INCURABLE ADVANCED STAGE NASOPHARYNGEAL CARCINOMA

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Nasopharyngeal carcinoma (NPC) represents a distinctive type of squamous cell carcinoma of the head and neck area (SCCHN). According to WHO histological classification, approximately 95% of all newly diagnosed cases are non-keratinized poorly-or un-differentiated type in Southern China or in other endemic regions. Together with the abundant lymphatic and vascular network in the post-nasal space, NPC has a propensity of regional and distant metastasis as compared to other types of SCCHN.

There has been shown that 30% and 20% of patients with limited disease treated definitively using conventional radiation therapy will develop distant and local recurrence, respectively. As recent advances in the treatment strategy and technique such as intensity-modulated radiation therapy (IMRT) and concurrent chemoradiotherapy have significantly improved the local and regional control of the disease, distant metastasis becomes an important mode of treatment failure.

Clearly, effective treatment strategies and regimens for patients with metastatic NPC are urgently needed. However, available data suggested that single agent or combination chemotherapy provided only palliative effects to patients with advanced stage NPC, and potential treatment options such as molecular targeted therapy and immunotherapy are in its infancy of research for NPC. The aim of this review is to discuss the currently available options of systemic treatment for incurable recurrent and metastatic NPC, with a brief introduction to future directions of research.

PROGNOSTIC FACTOR

For patients with recurrent or metastatic disease, except a small proportion could be managed by locoregional lymph node dissection or re-irradiation, most of them are unable to be cured. NPC is a relatively chemo-sensitive disease and chemotherapy confers variable degrees of palliative benefit. Based on the available evidence, the median overall survival ranged from 12 to 18 months for patients on palliative chemotherapy. Because the standard chemotherapy regimen remains uncertain, the establishment of prognostic factor appears to be helpful to compare different regimens and guide individualized management. In a study of 172 patients, Toh et al were able to validate a previously designed model and segregate patients into three prognostic categories based on independent variables including performance status, hemoglobin level, disease-free interval and metastasis at diagnosis. Recently, Wang et al found that the $t_{1/2}$ of plasma EBV DNA clearance measured by a real-time quantitative PCR in patients on palliative chemotherapy significantly correlated with complete response and overall survival. The author suggested this information could be informative to consider early change of chemotherapy regimen.

CHEMOTHERAPY

Cytotoxic chemotherapy is the mainstay treatment for the patients with incurable recurrent or metastatic NPC. So far, there was no phase Ⅲ randomized study that has been performed in this field. Therefore, although platinum-based chemotherapy is most commonly used, the optimal regimen remains uncertain. The selection of agents was largely determined by the patient characteristics, prior drug exposure and consideration of toxicity profiles.

Platinum and fluoropyrimidines

The preclinical and clinical evidence for the efficacy of cisplatin and 5-FU (PF regimen) in the curative-intent treatment of NPC is substantial. Therefore, PF regimen is considered to be a reasonable option in the palliative setting. In a phase Ⅱ study conducted in Singapore, 24 chemotherapy-naïve patients were treated with cisplatin at 100mg/m^2 in divided doses on days 1 to 3, and 5-FU 1000mg/m^2 daily by continuous infusion on days 1-5, every 3 weeks. Sixteen patients responded to the chemotherapy leading to an overall response rate of 66%. The median time to progression and overall survival were 8 and 11

months, respectively. There was no treatment-related mortality and common grade 3/4 toxicity was granulocytopenia, occurring in 41% of patients. With the goal of reducing cisplatin related toxicity such as nephrotoxicity, carboplatin was also combined with 5-FU and studied in 42 patients. Although the overall response rate was lower at 38%, the median survival of 12.1 months was acceptable. Therefore, in a palliative-intent setting, it seems reasonable to consider use of carboplatin, especially in patients with substantial cisplatin exposure during prior curative-intent treatment.

The oral fluoropyrimidine, capecitabine is proved to be alternative to infusional 5-FU in many gastrointestinal malignancies. Accordingly, in a phase Ⅱ study of 48 patients with metastatic disease, capecitabine was given at a dose of 1000mg/m^2 bid for 14 days in combination of cisplatin (80mg/m^2). There were 3 patients (6.3%) with complete response and 27 patients (56.3%) with partial response, giving an overall response rate of 62.5%. The median progression-free and overall survival were 7.7 and 13.3 months, respectively (Table 2-1). Besides in first-line, capecitabine was tested in salvage setting as monotherapy. In a retrospective study conducted by Chua et al, although 78% of enrolled patients had prior 5-FU exposure, the response was observed in 37% of patients. The median progression-free and overall survival were 5 and 14 months, respectively. Hand-foot syndrome (HFS), seen in 86% of patients, was severe grade in 25%. This capecitabine-induced typical toxicity was especially obvious at a dose of 1250mg/m^2 bid for 14 days in the first of 37 patients. A dose reduction to 1000mg/m^2 given in the same schedule reduced the incidence and severity of HFS in the final 12 patients. Although the comparison study between 5-FU and capecitabine is lacking, the convenience of oral administration and the avoidance of prolonged intravenous infusion make capecitabine an attractive selection of fluoropyrimidines.

Table 2-1 Studies using platinum and fluoropyrimidines

Study	Schedule	ORR (%)	Median OS (months)
Au et al	cisplatin 33mg/m^2 days 1-3 5-FU 1000mg/m^2 CIV days 1-5 cycles repeated every 3 weeks	66	11
Yeo et al	carboplatin 300mg/m^2 days 1 5-FU 1000mg/m^2 CIV days 1-3 cycles repeated every 3 weeks	38	12.1
Li et al	cisplatin 80mg/m^2 day 1 capecitabine 1000mg/m^2 bid days 1-14 cycles repeated every 3 weeks	62.5	13.3

Platinum-based multidrug regimens

Since NPC is sensitive to a variety of cytotoxic agents, some regimens combined more than 2 agents trying to improve the efficacy. The addition of bleomycin, a drug devoid of hematologic toxicity, to PF regimen was studied by a European and an Asian group with contrasting results. Boussen et al observed an overall response rate of 79% (19% complete). However, both the overall and complete response rates were much lower in the trial by Su et al at 40% and 3%, respectively. The survival data was not reported in either study. This obvious disparity is probably due to the different treatment schedules and patient selection. Anthracyclines, including doxorubicin and epirubicin, were also shown to be effective in NPC. One regimen named as "CAPABLE" which consisted of cyclophosphamide, doxorubicin, cisplatin, methotrexate, and bleomycin were tested in a phase Ⅰ/Ⅱ study. Ninety patients were enrolled and divided into 3 groups (21 with very advanced locoregional disease, 18 with persistent and/or recurrent disease postradiotherapy, and 51 with metastatic disease). The overall response rates were 86%, 41% and 80%, respectively. Responsive patients in the first group received subsequent radiotherapy, which may be responsible for the longest median survival (47 months) compared with 16 and 14 months in the other 2 groups. Although this complicated regimen is highly efficacious for NPC either with locoregional or with metastatic disease, the toxicity is substantial. Seven patients died of treatment-related complications and 37 required at least one hospital admission. Thus it is difficult to address the role of this aggressive regimen, especially when the aim of treatment is palliative.

Taxane-based regimens

The taxanes, including paclitaxel and docetaxel, are effective in a variety of cancer types including NPC. Paclitaxel is usually combined with carboplatin because of non-overlapped toxicities and convenient administration. Two studies used paclitaxel and carboplatin in patients with recurrent or metastatic NPC as first-line chemotherapy (Table 2-2). The response rates were 59% and 75%, respectively. The median overall survival (13.9 and 12 months) seemed to be comparable to that achieved by PF regimen. Neutropenia was the most common hematologic toxicity developed in about 1/3 of patients and non-hematologic toxicity was infrequent. This regimen also showed salvage efficacy for patients who failed cisplatin and 5-FU. In a small study performed by Airoldi et al, 12 heavily treated patients received salvage chemotherapy with paclitaxel and carboplatin. The response rate was 33.3% and median survival was 9.5 months. Therefore, for patients with recurrent and metastatic NPC, paclitaxel plus carboplatin is a reasonable regimen in first-line. Although its administration is more convenient than that of PF regimen, the

Table 2-2 Studies using taxane-based regimens

Study	Schedule	ORR (%)	Median OS (months)
Yeo et al	paclitaxel 135mg/m^2 day 1 carboplatin AUC 6 day 1 cycles repeated every 3 weeks	59	13.9
Tan et al	paclitaxel 175mg/m^2 day 1 carboplatin AUC 6 day 1 cycles repeated every 3 weeks	75	12
Airoldi et al	paclitaxel 175mg/m^2 day 1 carboplatin AUC 5.5 day 1 cycles repeated every 3 weeks	33.3	9.5
McCarthy et al	docetaxel 75mg/m^2 day 1 cisplatin 75mg/m^2 day 1 cycles repeated every 3 weeks	22	76% (1-y)
Chua et al	docetaxel 60-75mg/m^2 day 1 cisplatin 60-75mg/m^2 day 1 cycles repeated every 3 weeks	62.5	12.4

equivalence or superiority of efficacy needs to be confirmed in a randomized trial. For patients who have cisplatin-refractory disease, it could be a salvage regimen, but the necessity of carboplatin remains to be clarified.

Docetaxel is semi-synthesis taxane which showed stronger anti-neoplastic ability than paclitaxel in preclinical models. In studies for NPC, docetaxel is usually combined with cisplatin(Table 2-2). McCarthy et al from Canada conducted a phase Ⅱ study in patients with recurrent or metastatic NPC. After treatment of 9 patients, the accrual had to be stopped largely due to unacceptable toxicity. Although 2 patients responded to the treatment, all patients developed grade 3/4 neutropenia and 3 patients had neutropenic fever. On the contrary, another study from Hong Kong found the toxicity of this regimen with a lower dose (60mg/m^2) for both agents was manageable. Among 19 patients in this study, initial 15 patients were treated with 75mg/m^2 of both agents and subsequent 4 patients with 60mg/m^2. In patients on higher dose, the rate of febrile neutropenia occurred was 42%, but didn't occur in patients on lower dose. For total population, the response rate was 62.5% and median survival exceeded 1 year. The non-hematologic toxicity appeared to be mild in abovementioned studies.

In summary, both paclitaxel and decetaxel demonstrated high efficacy in patients with recurrent or metastatic NPC, when combined with platinum. Paclitaxel could be safely used with either carboplatin or cisplatin. If decetaxel is selected, the regular dose needs to be reduced and combination of carboplatin is a bit inappropriate due to overlapped toxicity of bone marrow suppression, especially if marrow growth factor support is not given.

Gemcitabine-based regimens

Gemcitabine is an antimetabolite with a broad-spectrum anti-neoplastic property. Although gemcitabine has not been intensively studied in head and neck cancer of other primary mucosal sites, it is highly effective in the treatment of NPC. So far, multiple studies using gemcitabine-based regimen have been done in first-line or salvage setting (Table 2-3). In a phase Ⅱ study from Hong Kong, 44 patients with recurrent or metastatic NPC were treated with gemcitabine plus cisplatin. Among them, 1/3 of patients received a prior cisplatin-based combination at least 6 months before study entry. The complete and partial responses were 20.5% and 52.3%, respectively. Impressively, none of patients had progressive disease during treatment. One year progression-free and overall survival rates were 36% and 62%, respectively. The chemotherapy was well-tolerated without treatment-related mortality. The grade 3/4 anemia, granulocytopenia and thrombocytopenia were found in 11, 37% and 16% of cycles, respectively.

Table 2-3 Studies using gemcitabine-based regimens

Study	Schedule	ORR (%)	1-year OS (%)
Ngan et al	gemcitabine 1000mg/m^2 days 1, 8, 15 cisplatin 50mg/m^2 days 1, 8 cycles repeated every 4 weeks	72.8	62
Zhang et al	gemcitabine 1000mg/m^2 days 1, 8, 15 cycles repeated every 4 weeks	43.8	67
Foo et al	gemcitabine 1250mg/m^2 days 1, 8 cycles repeated every 3 weeks	38	20 (1st line) 46 (salvage)
Wang et al	gemcitabine 1000mg/m^2 days 1, 8 vinorelbine 20mg/m^2 days 1, 8 cycles repeated every 3 weeks	36	46
Leong et al	gemcitabine 1250mg/m^2 days 1, 8 paclitaxel 70mg/m^2 days 1, 8 carboplatin AUC 5 cycles repeated every 3 weeks	78	83.5

Besides in the first-line setting, gemcitabine was also proved to be effective in the salvage setting for patients with platinum-refractory disease. Zhang et al from China conducted a phase Ⅱ study which enrolled 32 patients who had been pretreated with platinum-based chemotherapy. Single agent of gemcitabine was administered until progressive disease. Fourteen patients achieved partial response giving an overall response rate of 43.8%. The median time to progression and overall survival were 5.1 and 16 months, respectively. One year survival rate was 67% and only 12% of patients could survive for more than 2 years. The chemotherapy was unquestionably well-tolerated due to monotherapy. The most frequent grade 3/4 toxicity was neutropenia (18.7%) and non-hematologic toxicity was mild. Another study treated 52 patients with gemcitabine alone using a different schedule (1250mg/m^2 on days 1 and 8, every 3 weeks). Surprisingly, the response rate (48%) and median survival (10.5 months) achieved in pretreated patients were higher than those (28% and 7.2 months) in chemotherapy-naïve patients. It is too early to conclude that gemcitabine is more effective in the salvage setting. Certainly, possibility of selection bias in a non-randomized trial could not be entirely excluded. Wang et al combined gemcitabine with vinorelbine which is proved to be effective in other types of head and neck cancer in the salvage setting. The response rate was 36% and median response duration was 5.1 months. The median progression-free and overall survivals were 5.6 and 11.9 months, respectively. Regarding toxicity, the grade 3/4 neutropenia and thrombocytopenia developed in 44% and 18% of patients, respectively.

Because of the favorable toxicity profiles of gemcitabine, Leong et al proposed and tested a triplet regimen (gemcitabine, paclitaxel and carboplatin) in the first-line setting. Thirty-two patients with good performance status (ECOG PS 0-1) were enrolled in this phase Ⅱ trial. The median number of treatment cycles was 6 and overall response rate was 78%. The median time to progression and overall survival time were 8.1 and 18.6 months, respectively. The toxicity of this triplet regimen was pronounced. The dose reduction and omission were developed in a majority of patients largely due to the high rate of grade 3/4 neutropenia (79%). Moreover, 42% of patients experienced grade 3/4 anemia and thrombocytopenia. Although this study offered highest survival data so far, the considerable toxicity needs to be carefully monitored and managed. Since recurrent and metastatic NPC is generally incurable, patient selection and dose modification appear to be important for this aggressive regimen.

Irinotecan

Irinotecan is a topoisomerase I inhibitor licensed in gastrointestinal cancer. Recently, it was shown to be effective in other cancer including NPC. In a phase Ⅱ study from Singapore, twenty-eight patients with metastatic disease were treated with up to 6 cycles of irinotecan single agent (1000mg/m^2 on days 1, 8 and 15, cycles were repeated every 4 weeks). The response rate was 14% with duration of response ranging from 5.6 to 12.2 months. The median overall survival was 11.4 months which seems to be questionable, since the median follow-up was short at 7.5 months. The role of irinotecan needs to be investigated in additional clinical trials in NPC and its administration could not be routinely recommended in daily practice.

TARGETED THERAPY

The epidermal growth factor receptor (EGFR) as a therapeutic target had been studied in NPC. Similar to other squamous carcinoma occurred in the head and neck region, NPC confers a high expression of EGFR which may be associated with poor prognosis. Cetuximab, a human-mouse chimeric monoclonal antibody (mAb), was found to be synergistic with platinum *in vivo* study. Therefore, an exploratory phase Ⅱ trial using cetuximab plus carboplatin was conducted in 60 advanced patients who failed prior chemotherapy (mostly platinum) in an attempt to prove that cetuximab could reverse the drug-resistance. Cetuximab was administered at a loading dose of 400mg/m^2 followed by weekly doses of 250mg/m^2. Carboplatin area under the curve (AUC) 5 was administered every 3 weeks up to a maximum of eight cycles. Although the treatment was well-tolerated, the response rate was only 11.7%, most likely reflecting single-agent effects of cetuximab. Moreover, the median progression-free and overall survival was only 81 and 233 days, suggesting the poor prognosis in this patient cohort. Tyrosine kinase inhibitors including gefitinib and erlotinib were also studied in NPC, but the results were disappointing. In a phase Ⅱ study with 2 stage design, after first 19 patients were accrued and treated with gefitinib alone (500mg per day), the enrollment had to be discontinued due to lack of response. In summary, although EGFR inhibitor achieved success in the treatment of head and neck squamous carcinoma, there is no standard role in the treatment of NPC.

IMMUNOTHERAPY

Epstein-Barr virus (EBV) is uniformly detected in patients with undifferentiated and poorly-differentiated NPC and high virus DNA load after treatment was associated with poor prognosis. There is strong evidence that cytotoxic T lymphocyte (CTL)-based immunotherapy is effective in post-transplant lymphoproliferative disorders (PTLD) which is also EBV-associated. Therefore, multiple approaches of EBV-related immunotherapy are under active investigation in preclinical and clinical stages. Among these approaches, adoptive immunotherapy with autologous specific CTL therapy appears promising in limited experience. By this technique, 2 exploratory studies with similar protocol for patients with end stage NPC were reported. Both studies involved *ex vivo* expansions of EBV-specific CTLs through stimulation with EBV-transformed lymphoblastoid cell lines. Combining data from the

two studies, infusion of CTLs resulted in 2 complete and 3 partial response in a total of 16 patients with measurable disease, with response duration of 3-23 months. Moreover, 2 patients with stable disease were progression-free for 14 and 15 months. The toxicities were mild and well-tolerated. Clearly, this approach is worthy of further investigation. Efficacy may be improved by cytoreducing with chemotherapy prior to CTL infusion. Moreover, many issues need to be clarified and optimized, such as patient selection, CTL preparation and immunological regulation.

SUMMARY

Cytotoxic chemotherapy remains the treatment of choice for patients with incurable advanced stage NPC. In the past 5-10 years, taxanes and gemcitabine have demonstrated substantial efficacy and have been added to the armamentarium with platinum and fluoropyrimidines. Currently, platinum-based doublets appear to be generally well-tolerated and of palliative benefit. Monotherapy with a new class of agent could be considered as salvage treatment in patients with retained performance status. Randomized clinical trials for patients with incurable NPC are highly warranted and should stratify based-in-known prognostic factors. Targeted therapy was still under the stage of clinical investigation and new therapeutic targets need to be discovered and explored. Given the near universal association with EBV, virus-based immunotherapy is attractive and limited experience suggested promising and lack of significant toxicity. However, its high requirement of expertise, facility and cost impedes broad clinical application or even large-scale clinical trials. Development of an international consortium at centers of excellence may help overcome these obstacles to progress.

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