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• 临床应用 •

调强放疗联合单药顺铂不同化疗方案同期治疗鼻咽癌的急性不良反应比较

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Comparison of Acute Toxicity between Intensity-modulated Radiotherapy with Cisplatin Alone Concurrent Chemotherapy Weekly and Every Three Weeks for Nasopharyngeal Carcinoma Patients

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Abstract: **Objective** To compare the acute toxicities and nutritional status between non-metastasis nasopharyngeal carcinoma(NPC) patients treated by intensity-modulated radiotherapy(IMRT) combined with 40 mg/m² cisplatin alone concurrent chemotherapy weekly and those treated by IMRT with 80-100 mg/m^2 cisplatin every three weeks. **Methods** A retrospective clinical data analysis was conducted on 45 patients with non-metastatic NPC. Patients received 40 mg/m² cisplatin weekly or 80-100 mg/m^2 cisplatin every three weeks, concurrently with IMRT. The National Cancer Institute Common Toxicity Criteria version 3.0 scale (CTCAE V3.0) was used to assess the chemotherapy and acute toxicities. The acute toxicities and nutritional status were analyzed statistically by *t*-test, Chi-Square test/Chi-Square Goodness-of-Fit test or Analysis of Variance (ANOVA). **Results** In 45 NPC patients treated by IMRT, 31 patients received 40 mg/m² cisplatin weekly and 14 patients received 80-100 mg/m^2 cisplatin every three weeks concurrently chemotherapy. The grade 3-4 acute toxicity occurrence rates of xerostomia, pharyngodynia, oral mucositis, dermatitis, nausea, vomit and myelosuppression were 6.7%, 15.6%, 28.9%, 6.7%, 8.9%, 13.3% and 22.2%, respectively. Although the changes of BW, BMI, ALB, TP, BUN, Cr, Na^+, K^+, Ca^{2+} and Cl^- had no statistical difference between two groups after treatment($P>0.05$) by Gender stratification ANOVA, the change of ALB was closed to a statistical difference. Both groups of ALB, TP, Na^+ and Cl^- were decreased after treatment ($P<0.05$), but BW and BMI in cisplatin weekly group were decreased more severely than those in cisplatin every three weeks group. **Conclusion** It seems that the nutritional status of cisplatin weekly group is decreased more generally than that of cisplatin every three weeks group, but without significant difference in two groups before and after treatment.

Key words: Nasopharyngeal neoplasms; Cisplatin; Radiotherapy; Intensity-modulated; Concurrent chemoradiotherapy; Acute adverse reaction

摘　要：目的　比较无远处转移鼻咽癌（nasopharyngeal carcinoma, NPC）调强放疗（intensity-modulated radiotherapy，IMRT）联合单药顺铂每周（40 mg/m^2，1次/周）和每3周（80~100 mg/m^2，1次/3周）同期放化疗的急性不良反应和治疗前后的营养状况差异。**方法**　回顾分析45例IMRT联合单药顺铂同期化疗的非转移NPC患者临床资料，急性不良反应评估采用CTCAE 3.0标准，不良反应和营养状况统计分析采用*t*检验、卡方分析或精确概率法以及方差分析检验。**结果**　45例患者口干、咽痛、口腔黏膜炎、皮炎、恶心、呕吐及骨髓抑制3~4级不良反应发生率分别为6.7%、15.6%、28.9%、6.7%、8.9%、13.3%和22.2%。治疗后BW、BMI、TP、BUN、Cr、Na^+、K^+、Ca^{2+}和Cl^-变化的性别分层方差分析差异均无统计学意义（$P>0.05$），ALB变化接近统计学意义。组内分析显示两组治疗后ALB、TP、Na^+和Cl^-均下降（$P<0.05$），但顺铂每周组BW、BMI下降更明显（$P<0.05$）。**结论**　治疗前后两组营养

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状况均有不同程度下降，顺铂每周组营养失衡较顺铂每3周组更普遍，但治疗前后两组变化无明显差异。

关键词：鼻咽肿瘤；顺铂；放射疗法，高频；同期放化疗；急性不良反应

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0 引言

目前顺铂为主的同期放化疗是局部晚期鼻咽癌（nasopharyngeal carcinoma，NPC）的主要根治方案，调强放疗（intensity-modulated radiotherappy，IMRT）既能提高肿瘤靶区适形度、保护风险器官，还能减轻急性、晚期不良反应发生率和改善生活质量[1-2]，甚至能提高肿瘤局部控制率和总生存率[3-4]，因此，IMRT联合单药顺铂同期化疗逐渐成为NPC主流治疗模式。最新版美国NCCN指南和2010年NCCN指南（中国版）头颈部肿瘤临床实践指南推荐放疗联合单药顺铂同期化疗作为NPC首选治疗方案[5]，单药顺铂同期化疗方案有两种推荐，100 mg/m^2，1次/3周和40 mg/m^2，1次/周。本研究回顾分析IMRT联合指南推荐的单药顺铂方案同期化疗NPC患者的临床资料，比较单药顺铂每周方案（40 mg/m^2，1次/周）和每3周方案（100 mg/m^2，1次/3周）的急性不良反应和治疗前后患者的营养状况变化，探索两种同期放化疗方案对NPC患者的不同影响，为临床治疗提供依据。

1 资料与方法

1.1 研究对象

广西壮族自治区人民医院肿瘤中心放疗科2007年11月至2010年11月收治的无远处转移、IMRT联合单药顺铂同期化疗的NPC患者为研究对象，收集整理相关临床资料，符合研究标准并具有完整研究资料的患者共45例。

1.2 调强放疗方式

采用头后伸仰卧位，头颈肩面罩固定，增强CT扫描（颅顶至锁骨头下2 cm，2~3 mm /层），计划系统采用Nucletron或CMS。影像资料可见肿瘤为原发灶（GTVnx）和淋巴结区（GTVnd），GTVnx、GTVnd外扩3~5 mm为临床肿瘤体积（CTVnx/nd）；临床肿瘤体积1（CTV1）包括颅底、上颌窦后部、鼻腔后1/3、后组筛窦、蝶窦下部、咽旁间隙、咽后间隙、翼突、翼腭窝以及阳性淋巴结的颈部分区；临床肿瘤体积2（CTV2）为阳性淋巴结区域以外的颈部和锁骨阴性淋巴结区。计划肿瘤体积（PTVs）为CTVs外扩2~5 mm，规避脑干、脊髓、晶体等器官，处方剂量为：PTVnx 68~78 Gy，PTVnd 68~76 Gy包括鼻咽部和（或）转移淋巴结残留加量，PTV1 55.8~68 Gy，PTV2 50.4~60 Gy，分割剂量1.8~2.3 Gy/d，5次/周。

1.3 同期化疗方案

45例NPC患者均为单药顺铂同期化疗，31例患者采用40 mg/m^2，1次/周，平均化疗（5.2±1.4）周期，其中1例3周期同期化疗后因严重不良反应改为奈达铂单药，同期化疗6周期；另外14例患者采用80~100 mg/m^2，1次/3周，平均化疗（2.2±0.6）周期。同期化疗于IMRT第1或第2天开始。

1.4 研究方法

收集45例NPC患者IMRT前后体重、身高、营养元素和不良反应等临床资料，由公式计算身体质量指数（BMI）=体重/身高^2。比较分析放疗前后患者体重、BMI及营养状况变化和不良反应。放化疗急性不良反应评估采用CTCAE 3.0标准。

1.5 统计学方法

采用IBM SPSS20.0统计软件包，实验数据正态分布以（$\bar{x}\pm s$）表示，数据比较用两独立样本t检验和方差分析，非正态分布数据分析采用卡方检验或Fisher精确检验，$P<0.05$为差异有统计学意义。

2 结果

2.1 IMRT联合单药顺铂每周和每3周同期化疗方案一般情况比较

两组患者除性别外，年龄、病理分级、PS评分、T、N、M分期和临床分期组间差异均无统计学意义，见表1。

治疗方案显示两组患者顺铂总剂量存在组间差异，而放疗靶区PTVnx、PTVnd、PTV1、PTV2放疗剂量均无组间差异。

2.2 IMRT联合单药顺铂每周和每3周同期化疗的不良反应比较

本研究45例NPC患者口干、咽痛、口腔黏膜炎、皮炎、恶心、呕吐及骨髓抑制3~4级不良反应发生率分别为6.7%、15.6%、28.9%、6.7%、8.9%、13.3%和22.2%。31例单药顺铂每周和14例每3周同期放化疗患者0~2级和3~4级口干、咽痛、口腔黏膜炎、皮炎、恶心、呕吐及骨髓抑制等不良反应差异均无统计学意义（$P>0.05$），其中咽痛及呕吐反应接近统计学意义。性别分层方差分析提示两组患者放化疗不良反应差异均无统计学意义（$P>0.05$），见表2。

2.3 IMRT联合单药顺铂每周和每3周同期化疗NPC患者的营养状况比较

表1 45例鼻咽癌患者的一般临床特点和治疗方案 (*n* =45)

Table1 General clinical characteristics and treatment of NPC patients (*n* =45)

Characteristics	*n*		χ^2	*P*
	Cisplatin weekly	Cisplatin every three weeks		
Gender Male/Female	21/10	5/9	4.055	0.044
Age(years) ≥50/<50	11/20	4/10	0.013	0.909
Histology WHO 1 / WHO 3	2/29	0/14	-	1
Performance status 0/1/2	10/19/2	1/13/0	4.208	0.124
T stage			4.008	0.250
1	3	0		
2a+2b	11	2		
3	10	6		
4	7	6		
N stage			1.923	0.675
0	2	1		
1	7	3		
2	18	10		
3	4	0		
M stage			-	-
0	31	14		
1	0	0		
Clinical stage			1.564	0.466
Ⅰ	0	0		
Ⅱ	2	0		
Ⅲ	19	7		
Ⅳ	10	7		
Treatment			*t*	*P*
Radiotherapy dose (Gy)				
PTV-nx	70.587±2.295	72.000±2.936	–1.895	0.065
PTV-nd	70.059±1.428	70.427±1.399	–0.508	0.4253
PTV1	60.592±2.341	61.043±3.103	–0.109	0.9135
PTV2	54.392±2.095	54.914±2.158	–0.768	0.4468
Total cisplatin dose (mg)	313.548±81.550	264.286±44.500	2.611	0.013

Notes: NPC: nasopharyngeal carcinoma

除了顺铂每周方案的血清肌酐外，两组方案治疗后营养元素值均较治疗前有不同程度下降。统计分析显示IMRT联合两种单药顺铂同期化疗方案治疗前患者BW、BMI、ALB、TP、BUN、Cr、Na^+、K^+、Ca^{2+}和Cl^-差异无统计学意义（$P>0.05$）。组内比较显示，两组治疗后ALB、TP、Na^+和Cl^-较治疗前下降（$P<0.05$），顺铂每周组BW、BMI下降更明显（$P>0.05$）。性别分层方差分析显示，治疗前后两组BW、BMI、TP、BUN、Cr、Na^+、K^+、Ca^{2+}和Cl^-变化差异均无统计学意义（$P>0.05$），ALB变化差异接近统计学意义，见表3。另外，顺铂每周方案组有1例出现一过性急性肾功能不全，3周方案组无肾功能异常出现。

表2 鼻咽癌调强放疗联合单药顺铂每周和每3周方案同期化疗的不良反应比较 (*n*=45)

Table2 Toxicity of IMRT combined with cisplatin alone concurrent chemotherapy weekly and every three weeks for NPC patients (*n*=45)

Toxicity grade	*n*		χ^2	*P*	Gender ANOVA	
	Cisplatin weekly	Cisplatin every 3-week			χ^2	*P*
Xerostomia			-	0.541	0.350	0.554
0-2	28	14				
3	3	0				
Pharyngodynia			-	0.081	2.108	0.147
0-2	24	14				
3	7	0				
Oral mucositis			0.000	1	0.062	0.803
0-2	22	10				
3-4	9	4				
Dermatitis			-	1	0.350	0.554
0-2	29	13				
3	2	1				
Nausea			-	0.578	0.040	0.842
0-2	29	12				
3	2	2				
Vomit			-	0.065	2.343	0.126
0-2	29	10				
3	2	4				
Myelosuppression			0.224	0.636	0.304	0.581
0-2	23	12				
3-4	8	2				

Notes: IMRT: intensity-modulated radiotherapy

3 讨论

目前研究显示局部晚期NPC辅助化疗并未带来生存获益，尽管诱导化疗联合同期放化疗被NCCN指南推荐，但其作用和地位尚未被完全肯定[6-7]。单药顺铂同期放化疗仍是NPC的标准治疗方案。文献报道IMRT联合单药顺铂同期放化疗使NPC患者5年总生存率提高至80%左右，早期患者5年生存率高于95%，部分报道达100%[8-9]。研究显示顺铂同期化疗的总剂量与NPC患者的总生存率和无复发生存率有关[10]。还有研究发现Ⅱ、Ⅲ期同期放化疗的NPC患者，顺铂每周同期化疗5周期以上、总剂量 > 200 mg/m^{2}者的总生存明显高于5周期以下、顺铂总剂量 < 200 mg/m^{2}的患者[11]，提示顺铂同期化疗的总剂量与疗效相关。Chen的研究显示，与单纯放疗比较，顺铂同期放化疗可以提高Ⅱ期NPC的5年总生存率、无病生存率以及无远处转移生存率，但没有提高局部和区域控制率，而白细胞减少、口腔黏膜炎、恶心和呕吐等急性不良反应明显增加，晚期不良反应增加不明显[12]。还有研究也显示单药顺铂同期放化疗能提高局部晚期NPC患者的总生存率，

表3　IMRT联合单药顺铂每周和每3周同期放化疗NPC患者的营养状况比较（n=45）

Table3　Nutritional status of IMRT combined with cisplatin alone concurrent chemotherapy weekly and every three weeks for NPC patients (n=45)

Nutrition	Cisplatin weekly		t	P	Cisplatin every three weeks		t	P	Pre-RT^a *vs.* Pre-RT^b		Post-RT^c *vs.* Post-RT^d		Pre-RT^a—Post-RT^c *vs.* Pre-RT^b—Post-RT^d	
	Pre-RT^a	Post-RT^c			Pre-RT^b	Post-RT^d			F	P	F	P	$F^▲$	$P^▲$
BW	60.177±8.601	53.807±7.645	3.083	0.003	58.393±9.443	55.107±9.731	0.907	0.373	3.430	0.071	7.239	0.010	1.625	0.210
BMI	22.839±2.777	20.414±2.540	3.588	0.001	21.908±2.754	20.651±2.826	1.192	0.244	2.710	0.107	5.702	0.022	1.432	0.238
ALB	42.739±2.757	38.426±3.513	5.377	0.000	42.150±2.751	39.057±2.558	3.081	0.005	0.970	0.330	1.180	0.284	3.387	0.073
TP	71.168±5.604	66.668±5.105	3.305	0.002	70.657±3.426	65.379±4.014	3.743	0.001	0.082	0.776	1.345	0.253	2.120	0.153
BUN	3.950±1.202	3.895±1.814	0.141	0.888	4.903±2.096	3.651±1.353	1.877	0.072	0.406	0.528	0.775	0384	0.065	0.800
Cr	75.032±14.992	75.839±19.400	-0.183	0.855	75.929±24.110	73.500±13.592	0.328	0.745	0.004	0.948	2.446	0.125	1.416	0.241
Na^+	140.839±2.672	137.000±2.910	5.410	0.000	140.857±3.860	137.929±2.495	2.384	0.026	0.125	0.725	0.945	0.337	0.721	0.401
K^+	4.027±0.486	3.820±0.422	1.788	0.079	4.024±0.276	3.636±0.322	3.417	0.002	0.169	0.683	0.240	0.627	0.552	0.462
Ca^{2+}	2.326±0.118	2.270±0.173	1.500	0.139	2.362±0.118	2.309±0.136	1.112	0.276	0.154	0.697	0.033	0.857	0.252	0.619
Cl^-	103.452±2.987	99.516±3.957	4.420	0.000	104.214±3.641	100.929±2.947	2.624	0.014	0.032	0.858	0.238	0.598	0.244	0.624

Notes: Pre-RT^a: before IMRT with cisplatin weekly; Pre-RT^b: before IMRT with cisplatin every 3 weeks; Post-RT^c: after IMRT with cisplatin weekly; Post-RT^d: after IMRT with cisplatin every 3 weeks; Pre-RT^a—Post-RT^c: variation of Pre-RT^a and Post-RT^c; Pre-RT^b—Post-RT^d: variation of Pre-RTb and Post-RT^d; BW: body weight; BMI: body mass index=BW/body height^2; ALB: serum albumin; BUN: serum urea nitrogen; TP: serum total protein; Cr: serum creatinine; Na^+: serum Na^+; K^+: serum k^+; Ca: serum Ca^{2+}; Cl^-: serum Cl^-; $F^▲$ and $P^▲$: Gender ANOVA

但不良反应发生率也明显增加，尤以3~4级血液学毒性和口黏膜炎最为常见[6, 13-15]。Liu发现，与单纯放疗比较，同期放化疗能提高成人合并症评测-27（ACE-27）评分小于2分的老年NPC患者5年总生存率、肿瘤特异性生存率和无病生存率，但无转移生存率无明显提高，而对2分以上老年患者5年总生存率无明显改善[16]。极少数研究显示顺铂同期放化疗对NPC总生存改善不明显，反而增加了严重不良反应[9]，甚至提高了死亡风险[17]。本研究组前期研究IMRT联合顺铂每周同期化疗显示95.5%患者可完成既定方案治疗，22例患者3~4级口腔黏膜炎发生率达27%，其余3~4级急性不良反应发生率小于10%[18]。由此可见，多数研究认为鼻咽癌顺铂同期放化疗的疗效值得肯定，但同期放化疗的急性不良反应发生率高于单纯放疗，值得重视。另外，顺铂同期化疗的总剂量可能与NPC预后有关。高效、低毒、合理的NPC同期放化疗方案仍待探索。

本研究比较无远处转移NPC患者IMRT联合两种单药顺铂同期化疗的急性不良反应和营养状况，结果显示45例患者口腔黏膜炎和骨髓抑制3~4级不良反应超过20%，其余均小于20%，与文献报道类似。单药顺铂每周和每3周同期化疗的口干、咽痛、口腔黏膜炎、皮炎、恶心、呕吐及骨髓抑制0~2级和3~4级不良反应差异无统计学意义，提示两种方案联合IMRT的急性不良反应基本类似。营养状况比较结果显示，治疗后BW、BMI、ALB、TP、BUN、Na^+、K^+、Ca^{2+}和Cl^-均有不同程度下降，但两组同期放化疗方案无组间差异。组内分析结果提示顺铂每周同期化疗组BW、BMI减轻以及营养不良状况似乎较3周组更明显，可能与每周同期化疗时顺铂的总剂量较高有关，还有可能因为每周同期化疗时顺铂累积毒性和持续作用，导致患者恶心、呕吐以及食欲不振，治疗期间营养摄入减少有关。不少研究显示NPC患者放化疗期间会出现不同程度的营养不良及体重减轻[19-22]。还有研究报道鼻咽癌IMRT患者营养状况改变可能影响IMRT计划[23-24]。可见，IMRT联合顺铂同期放化疗NPC患者的营养状况变化值得重视。

总之，顺铂同期放化疗提高了NPC患者的总生存率，但同期放化疗的急性不良反应较单纯放疗明显增加。鼻咽癌IMRT联合单药顺铂每周和每3周同期放化疗的急性不良反应差别可能不明显，但治疗前后均有不同程度营养失衡，似乎单药顺铂每周同期化疗方案营养状况改变较3周方案更普遍，而两种方案疗效差异有待比较。由于样本量和回顾性研究方法等因素限制，鼻咽癌高效、低毒、安全、合理的单药顺铂同期放化疗方案有待多中心、大样本、前瞻性临床研究证实。

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