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培美曲塞与吉西他滨联合卡铂治疗初治老年晚期肺腺癌的临床观察 *

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摘要 目的:比较培美曲塞与吉西他滨联合卡铂治疗初治老年晚期肺腺癌的疗效和安全性。**方法:**收集 2010 年 1 月 -2011 年 12 月我院≥ 65 岁的Ⅲb 期和Ⅳ期肺腺患者 84 例,随机分为培美曲塞联合卡铂(PC)组:培美曲塞 500 mg / m^2 d1,卡铂按曲线下面积(Auc)=5 的剂量水平 d2;吉西他滨联合卡铂(GC)组:吉西他滨 1000 mg / m^2 d1,8,卡铂按 Auc=5 的剂量水平 d2,两组 1 个治疗周期均为 21 d,每组 42 例,比较两组患者的有效率,不良反应及 1、2 年生存率。**结果:**PC 组和 GC 组总有效率分别为 28.6% 和 19% (P<0.05),疾病控制率分别为 73.8%和 57.1% (P<0.05);两组的中位 PFS 分别为 11.8 个月和 10.2 个月(P>0.05),1 年生存率分别为 52.3%和 51.2% (P>0.05),2 年生存率分别为 24.1% 和 22.4% (P>0.05);PC 组患者白细胞减少、贫血及血小板减少的不良反应发生率均明显低于 GC 组 (P<0.05)。**结论:**培美曲塞联合卡铂与吉西他滨联合卡铂对初治老年晚期肺腺癌的疗效相近,但前者可能更安全;PC 方案可作为老年晚期肺腺癌有效的一线化疗方案。

关键词:肺腺癌;培美曲塞; 吉西他滨;卡铂

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Efficacy of Pemetrexed or Gemcitabine Combined with Carboplatin in the Treatment of Elderly Patients with Advanced Lung Adenocarcinoma*

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ABSTRACT Objective: To compare the efficacy and safety of pemetrexed or gemcitabine combined with carboplatin in the treatment of elderly patients with advanced lung adenocarcinoma. **Methods:** From January 2010 to December 2011 in our hospital, 84 elderly patients (≥ 65) with stage Ⅲb and Ⅳ lung adenocarcinoma were collected, and randomly divided into pemetrexed plus carboplatin group(PC) with 42 cases and gemcitabine plus carboplatin group(GC) with 42 cases. PC group was received pemetrexed 500 mg /m^2 d1 and carboplatin in the area under the curve (Auc) of =5 d2, whereas GC group was recieved gemcitabine 1000 mg/m^2 d1,8, and carboplatin at a dose of Auc=5 level d2. One treatment cycles were 21 days. The efficiency, adverse reactions and 1, 2 year survival rate were compared. **Results:** The total effective rates in PC group and GC group were 28.6% and 19% (P<0.05) respectively. The disease control rates were 73.8% and 57.1% (P<0.05). The median PFS were 11.8 and 10.2 months(P>0.05).1 year survival rates were 52.3% and 51.2% (P>0.05). 2 years survival rates were 24.1% and 22.4% (P>0.05). In the PC group,?leukopenia, anemia and thrombocytopenia were significantly lower than those in the GC group (P<0.05). **Conclusion:** The efficacy of pemetrexed or gemcitabine combined with carboplatin in the treatment of elderly patients with advanced lung adenocarcinoma was roughly similar, but the former may be less adverse reactions. Therefore pemetrexed combined with carboplatin can be used as a safe and effective drug for clinical first-line treatment for the elderly patients with advanced lung adenocarcinoma.

Key words: Lung adenocarcinoma; Pemetrexed; Gemcitabine; Carboplatin

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前言

据统计，目前确诊为晚期非小细胞肺癌(non-small-cell lung cancer,NSCLC)患者约 60% 年龄 >65 岁,由于丧失手术机会,其治疗手段主要为化疗。NSCLC 患者中约 40%为肺腺癌,对化疗药物较为敏感。第 3 代化疗药物如培美曲塞等与铂类的联合化疗是 NSCLC 的标准一线化疗方案[1]。目前临床上顺铂使用较普遍,但其消化道反应严重,肾毒性和耳毒性较大,大大限制了其在老年患者中的使用。卡铂为第 2 代铂类广谱抗肿瘤药物,其疗效与顺铂相当,但其不良反应较后者轻,患者耐受性

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良好[2]。为探索适合老年肺腺癌患者的化疗方案,因此我们比较了培美曲塞联合卡铂与吉西他滨联合卡铂治疗老年肺腺癌的疗效及不良反应。本研究方案经中南大学湘雅医学院附属肿瘤医院伦理委员会批准,并获得了良好的效果。

1 资料与方法

1.1 一般资料

收集 2010 年 1 月至 2011 年 12 月入住我院,年龄≥ 65 岁经病理学或细胞学确诊的肺腺患者 84 例。入选标准:①依据国际抗癌联盟(UICC)第 7 版恶性肿瘤的 TNM 分期标准为 IIIb 期或 IV 期的初治患者,或是接受手术后辅助化疗(未经培美曲塞、吉西他滨治疗)6 个月后复发者;②有影像学可客观测量的肿瘤病灶;③ ECOG 评分≤ 2 分,④预期生存时间应大于或等于 3 个月;⑤化疗前心电图、血常规及肝肾功能均正常。排除标准:① 患者主动要求退出,因而未完成计划内治疗者:② 出现不能耐受的并发症或病情进展者。84 例患者均签署知情同意书,采用随机数字方法分为培美曲塞联合卡铂(PC)组和吉西他滨联合卡铂(GC)组,每组各 42 例。治疗前 PC 组和 GC 组年龄分别为(70.12± 2.11)岁和(69.98± 2.53)岁、其它如性别、临床分期、ECOG 评分等均无明显差异(P>0.05),见表 1。

表 1 两组患者一般资料情况

Table 1 The characteristics of the two groups

Clinical data	PC group	GC group	P
n	42	42	
Gender			
Male	24(57.1%)	23(54.8%)	1.000
Female	18(42.9%)	19(45.2%)	
Age(year)	69.98± 2.53	70.12± 2.11	1.000
Clinical stage			
ⅢB	22(52.4%)	23(54.8%)	1.000
Ⅳ	20(47.6%)	19(45.2%)	
Treatment			
Initial treatment	16(38.1%)	15(37.7%)	1.000
Retreatment	26(61.9%)	27(62.3)	
ECOG scores			
0-1	32(76.2%)	30(71.4%)	0.804
2	10(23.8%)	12(28.6%)	

1.2 治疗方法

PC 组:培美曲塞(豪森制药)500 mg / m^2 d1,卡铂按曲线下面积(Auc)=5 的剂量水平 d2,化疗前 7d 直至化疗结束口服叶酸 400 μg/d,化疗前 1d 肌注维生素 B12 1mg,化疗前 1d 开始口服地塞米松 8mg/d,连续口服 3d;GC 组:吉西他滨(豪森制药)1000 mg / m^2 d1,8,卡铂按 Auc=5 的剂量水平 d2。两组保持用药平衡均合,PC 组和 GC 组每个治疗周期均为 21 d。

1.3 疗效及毒性反应评定标准

比较两组患者的有效率,不良反应及 1、2 年生存率:治疗 2 个周期后,使用 RECIST 标准评价疗效,假如 1 次化疗后患者主诉症状加重,也需评价疗效,首次评价完全缓解(complete response,CR)、部分缓解(partial response,PR)、稳定(stable disease,SD)后 4 周,再进行复核确认。总缓解率(RR)=100%×(CR+PR)/ 总例数,疾病控制率(DCR) =100%× CR+PR+SD/ 总例数。无进展生存期(PFS)定义为从化疗开始至疾病进展或死亡的时间。毒副反应按 NCI-CTC 3.0 常见毒性分级标准评价。

1.4 统计分析

采用 SPSS 19.0 软件进行统计分析,计数资料采用卡方检验(必要时采用 Fisher 精确检验),秩和检验比较组间临床特征、疗效及毒副反应的差异。生存时间的计算自治疗开始至死亡或末次随访日期止,生存分析采用 Kaplan-Meier 单因素方法。P<0.05 为差异具有统计学意义。

2 结果

2.1 临床疗效比较

82 例患者平均化疗 3.8 个周期,共化疗 304 个周期,治疗期间 PC 组和 GC 组均无脱落病例,均可评价疗效。

PC 组和 GC 组均无 CR 病例,PC 组 PR 12 例 (28. 6%),SD 19 例(45. 2%),PD 11 例(26.2%);GC 组 PR 8 例(19.0%),SD 16 例(38.1%),PD 18 例(42.9%),即 PC 组和 GC 组总有效率分别为 28. 6% 和 19%,疾病控制率分别为 73.8%和 57.1%,均有统计学意义(P<0.05),见表 2。

表 2 两组患者的临床疗效比较(例数,%)

Table 2 Clinical efficacy in patients (n, %)

Groups	n	PR	SD	PD	RR	DCR
PC group	42	12(28.6)	19(45.2)	11(26.2)	12(28.6)	31(73.8)
GC group	42	8(19.0)	16(38.1)	18(42.9)	8(19.0)*	24(57.1)*

注:与 PC 组比较,* P<0.05。

Note: comparison with pemetrexed group, * P<0.05.

2.2 生存情况比较

随访至 2013 年 11 月 30 日,PC 组和 GC 组的中位 PFS 分别为 11.8 个月和 10.2 个月 (P>0.05),1 年生存率分别为 52.3% 和 51.2% (P>0.05),2 年生存率分别为 24.1% 和 22.4% (P>0.05)。

2.3 毒副作用比较

PC 组和 GC 组患者均可评价毒副反应,主要表现为血液学毒性和消化道反应。其中 PC 组白细胞减少、贫血等血液学毒性发生率明显低于 GC 组,差异具有显著性统计学意义(P< 0.05)。两组患者化疗后不良反应发生情况比较,见表 3。

表 3 化疗后两组患者的不良反应(例)

Table 3 Comparison of the occurrence of adverse reactions in the two groups of patients after chemotherapy (n)

Adverse reactions	PC group (n=42)		GC group (n=42)		x^2	P
Leukopenia	18	42.9%	31	73.8%	9.340	0.001
Anemia	6	14.2%	15	57.45%	4.063	0.042
Thrombocytopenia	5	11.9%	14	33.3%	4.353	0.035
Nauseated and vomiting	7	16.7%	9	21.4%	0.077	0.782
Abnormal liver function	5	11.9%	9	21.4%	0.771	0.380

3 讨论

NSCLC 包括鳞癌、腺癌、大细胞癌等病理类型，约占肺癌总数的 80%～85%[3]，具有发病率高和死亡率高的特点。其发病率高主要与吸烟、环境因素恶化关系密切，死亡率高则与缺乏有效的早期筛查和早期诊断手段相关，多数患者一旦确诊，已处于Ⅲb 或Ⅳ期非小细胞肺癌，失去采取手术切除最佳治疗时间。相对与年轻患者，由于器官功能减退，且常有冠心病等多种伴发疾病，对于 >65 岁的老年肺腺癌患者，考虑其存在较高的治疗相关毒性反应风险，因此，临床医生在制定治疗方案时要综合考虑治疗效果及化疗带来的毒副反应。

目前 NSCLC 的标准一线化疗方案是第 3 代化疗药物与铂类的联合化疗[4]，多项研究表明培美曲塞联合卡铂治疗非鳞状非小细胞肺癌均取得较好的疗效[5-7]。本研究主要聚焦于第 3 代化疗药物培美曲塞和吉西他滨联合卡铂治疗晚期老年肺腺癌的疗效。

培美曲塞是继甲氨蝶呤和氟尿嘧啶之后新一代多靶点抗叶酸制剂[8,9]，通过作用于叶酸合成途径中酶 - 胸苷酸合成酶、二氢叶酸还原酶、甘氨酰胺甲酰基转移酶等多个酶，抑制肿瘤细胞 DNA 和 RNA 合成使肿瘤细胞分裂停滞于 S 期，从而抑制细胞增殖和肿瘤生长，具有高效、低毒的特点。2008 年 9 月，培美曲塞被美国食品药品管理局批准作为 NSCLC 的一线治疗用药。吉而西他滨是一种破坏细胞复制的二氟核苷类抗代谢物的药物，可引起骨髓抑制等不良反应。

顺铂是最常见第一代铂类药物，Yang 等研究发现采用培美曲塞联合顺铂治疗非鳞癌患者，其预后明显优于鳞癌患者，而采用吉西他滨联合顺铂方案治疗后鳞癌患者生存更有优势[10]。但是对于老年肺腺癌患者而言，其会导致严重消化道反应甚至肾脏、耳的毒性。第二代铂类广谱抗肿瘤药物卡铂疗效与顺铂相当，但胃肠道反应轻，患者耐受性良好。Rogerio C. Lilenbaum 等研究发现，相对与培美曲塞单药，培美曲塞联合卡铂方案用于晚期 NSCLC 的治疗，反应率为 23.8%，一年生存率达 40.1%，表明 PC 方案能明显提高晚期 NSCLC 的生成率[11]。

考虑到我国老年人的体质，为了减轻不良反应，根据 2008 年和 2009 年《NCCN 非小细胞肺癌临床实践指南(中国版)》[12,13]及文献[14]，本研究中吉西他滨的用量定为 1,000 mg / m^2。我们发现分别用 PC 方案与 GC 方案治疗晚期老年肺腺癌患者，前者的总有效率显著高于后者($P<0.05$)，血液系统的不良反应也比后者轻($P<0.05$)，但是其中位 PFS、1 年生存率和 2 年生存率没有明显差异，与既往文献相符[15,16]。与孙燕等[14]比较 GP 与 CP 两者疗效后所得研究结果大致相同，但毒副反应更轻[17-19]，说明培美曲塞比吉西他滨联合卡铂治疗肺腺癌近期疗效较好。值得注意的是，本研究与孙燕等人的研究相比，PC 方案比 GP 方案的毒副反应要轻，说明在经济条件许可的情况下，对于老年肺腺癌患者，卡铂更具耐受性[20,21]。

综上所述，培美曲塞比吉西他滨联合卡铂治疗肺腺癌近期疗效较好，且由于毒副作用相对较低，老年患者耐受性和依从性更好。相对于 PP 及 GC 方案，PC 方案可能更适合于初治的晚期老年肺腺癌患者，由于本研究选择病例数相对有限，值得临床继续研究和探讨。

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(下转第 5263 页)

研究中，我们将进一步细化分析各方位及角度牙齿的菌斑状况。

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