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艾迪注射液联合吉非替尼片治疗 EGFR 阳性晚期非小细胞肺癌的临床疗效观察

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摘要 目的：探讨艾迪注射液结合吉非替尼片治疗表皮生长因子受体（EGFR）阳性晚期非小细胞肺癌（NSCLC）的临床疗效。**方法：**选取 2012 年 1 月至 2015 年 12 月在航天中心医院和华中科技大学同济医学院附属普爱医院治疗的 EGFR 阳性晚期 NSCLC 患者 62 例，按照随机双盲法分为实验组和对照组各 31 例，实验组给予艾迪注射液联合吉非替尼片治疗，对照组单纯使用吉非替尼片治疗，两组均治疗 2 个疗程。比较两组患者的治疗效果及其不良反应的发生情况，随访 1 年，比较两组患者的存活率。**结果：**实验组有效率和疾病控制率高于对照组（P<0.05），实验组疼痛减轻率、睡眠质量改善率和饮食改善率较对照组升高（P<0.05），实验组不良反应的发生率稍低于对照组，但是差异无统计学意义（P>0.05）。随访 1 年发现实验组 28 例存活，对照组 22 例存活，实验组的存活率高于对照组（P<0.05）。**结论：**艾迪注射液联合吉非替尼片较单纯应用吉非替尼片治疗 EGFR 阳性晚期 NSCLC 的疗效更好，能够改善患者睡眠质量和饮食状况，减轻疼痛，用药安全性较好，从而改善患者的预后，值得临床推广。

关键词：吉非替尼片；艾迪注射液；EGFR；晚期；非小细胞肺癌；疗效；预后

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Clinical Observation of Gefitinib Tablets Combined with Addie Injection in the Treatment of Advanced Non-Small Cell Lung Cancer with EGFR Positive

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ABSTRACT Objective: To observe the clinical efficacy of Gefitinib tablets combined with Addie injection in the treatment of advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) positive. **Methods:** 62 cases of advanced NSCLC with EGFR positive patients treated in Aerospace Central Hospital and Puai Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology from January 2012 to December 2015 were selected. They were divided into experimental group (n=31) and control group (n=31) according to the randomized double blind method. The experimental group were treated with Addie injection combined with Gefitinib Tablets, and the control group were only treated with Gefitinib Tablets, the two groups were treated for 2 courses. The treatment effect and adverse reactions of the two groups were compared. Followed up for 1 year, the survival rate of the two groups was compared. **Results:** The effective rate and disease control rate in the experimental group were higher than those in the control group (P<0.05). The pain relief rate, improvement rate of sleep quality and diet improvement rate in the experimental group were higher than those in the control group (P<0.05). The incidence of adverse reactions in the experimental group was slightly lower than that in the control group, but the difference was not statistically significant (P>0.05). Followed up for 1 years, 28 patients in the experimental group survived, and 22 cases in the control group survived. The survival rate in the experimental group was higher than that in the control group (P<0.05). **Conclusion:** The curative effect of Addie injection combined with Gefitinib Tablets is better than simple application of Gefitinib Tablets in the treatment of EGFR positive advanced NSCLC, can improve sleep quality and diet condition, relieve pain, better safety, so as to improve the prognosis of patients, it is worthy of clinical promotion.

Key words: Gefitinib tablets; Addie injection; EGFR; Advanced; Non-small cell lung cancer; Curative effect; Prognosis

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前言

肺癌已成为目前最为致命的恶性肿瘤之一,在我国其发病率和死亡率排在所有恶性肿瘤的第一位。非小细胞肺癌(Non-Small Cell Lung Cancer, NSCLC)为肺癌最常见的类型,其患病人数达到肺癌总数的80%左右[1-3]。由于大部分肺癌患者早期无特异性症状,随着病情的发展,会逐渐出现咳嗽、痰中带血、咯血、胸痛等症状,但此时多数患者已处于肺癌晚期,近60%的患者初诊时已失去手术机会,无法进行手术的患者预后很差,中位生存期仅有8-10个月[4-6]。细胞毒化疗药物治疗效果十分有限,分子靶向药物为难治的NSCLC开辟了新的途径。吉非替尼片对转移性的NSCLC有较好的疗效和安全性[3],但目前各种癌症多采用综合治疗,从多个作用位点来最大限度的控制肿瘤[7,8]。艾迪注射液是一种中药制剂,具有清热解毒、消瘀散结的功效,常用于肺癌、肝癌、直肠癌等疾病的治疗[9,10]。随着国内外不断的研究,艾迪注射液用于NSCLC的治疗效果已经被发现,并得到认可[11]。本研究通过探讨艾迪注射液联合吉非替尼片治疗表皮生长因子受体(EGFR)阳性晚期NSCLC的疗效、不良反应及对预后的影响,旨在研究其在此类患者治疗中的临床价值,现作如下报道。

1 资料与方法

1.1 一般资料

选取2012年1月至2015年12月期间航天中心医院和华中科技大学同济医学院附属普爱医院收治入院的晚期NSCLC患者62例作为研究对象,纳入标准:(1)均经病理组织学或细胞学确诊为NSCLC,且EGFR均为阳性;(2)所有患者临床分期均处于Ⅲ~Ⅳ期,肺内存在可评价的肿瘤病灶;(3)经评估预计生存期≥ 3个月,Karnofsky评分≥ 60分;(4)患者的血常规以及心、肾、肝功能均正常;(5)若是复治病例,则无艾迪注射液以及吉非替尼治疗史,且与上次治疗的时间差≥ 1个月;(6)患者及其家属对本研究知情同意并签署知情同意书。排除标准:(1)合并有其他恶性肿瘤者;(2)妊娠期妇女;(3)依从性较差者;(4)随访失联者;(5)存在精神疾病者。按照随机双盲法原则将其分成对照组和实验组各31例。对照组男17例,女14例,年龄20-81岁,平均年龄(40.6± 8.5)岁,临床分期:Ⅲ期14例,Ⅳ期17例,病理类型:鳞癌10例,腺癌15例,鳞腺癌2例,大细胞癌4例,合并疾病:高血压10例,糖尿病7例,11例有吸烟史。实验组男19例,女12例,年龄22-82岁,平均年龄(44.5± 6.5)岁,临床分期:Ⅲ期12例,Ⅳ期19例,病理类型:鳞癌11例,腺癌12例,鳞腺癌4例,大细胞癌4例,合并疾病:高血压9例,糖尿病8例,13例有吸烟史。两组患者临床资料比较无统计学差异(P>0.05),表明数据具有可比性。本研究经航天中心医院和华中科技大学同济医学院附属普爱医院伦理委员会审核并批准实施。

1.2 治疗方法

实验组所有患者给予艾迪注射液(贵州益佰制药股份有限公司,国药准字Z52020236,规格:每支10 mL)100 mL,生理盐水稀释后静脉滴注,每日1次,30天为1个疗程,间隔10天,再进行下一个疗程。加用吉非替尼片(齐鲁制药(海南)有限公司,国药准字H20163465,规格:0.25 g)0.25 g,1日1次,口服,温开水送服,空腹或与食物同服。对照组单纯使用吉非替尼片治疗,服用方法同上。两组均治疗2个疗程。

1.3 观察指标

治疗期间对患者疼痛减轻、睡眠质量改善和饮食改善的情况进行记录,根据肺癌症状量表(LCSS)对患者的症状进行评价,主要观察患者疼痛、睡眠质量、饮食三个方面的情况,若某一方面治疗前后的评分差值大于25分,则可认为该方面得到改善,分值越高代表情况越好。参照WHO急性与亚急性毒性表现和分级标准统计两组患者的不良反应以及对比其不良反应发生率。随访1年,主要通过电话、预约门诊的方式进行随访,统计患者死亡例数并计算存活率。

1.4 疗效评价

治疗2个月后按照WHO实体瘤疗效评价标准进行疗效评价[12],分为完全缓解(CR):所有靶病灶消失,并且维持时间为4周或4周以上;部分缓解(PR):靶病灶双径乘积之和下降超过50%,并且维持时间为4周或4周以上;疾病稳定(SD):非CR、PR、PD;疾病进展(PD):靶病灶最大径之和与参考值比较扩大20%以上,或有新的病灶出现。有效率=[(CR+PR)/总病例]×100%。疾病控制率=[(CR+PR+SD)/总病例]×100%。

1.5 统计学方法

应用SPSS18.0进行统计分析,有效率、疾病控制率、存活率等计数资料以率(%)表示,进行x^2检验,平均年龄等计量资料采用($\bar{x}\pm s$)表示,进行t检验,将α=0.05作为检验标准。

2 结果

2.1 两组近期疗效比较

实验组有效率和疾病控制率分别为45.16%、80.65%,对照组有效率和疾病控制率分别为19.35%、51.61%,两组比较差异有统计学意义(P<0.05),见表1。

表1 两组患者近期疗效比较

Table 1 Comparison of short-term efficacy between the two groups

Groups	n	CR	PR	SD	PD	Effective rate (%)	Disease control rate(%)
Experimental group	31	0	14	11	6	45.16	80.65
Control group	31	0	6	10	15	19.35	51.61
x^2						4.724	5.833
P						0.030	0.016

2.2 两组临床治疗效果比较

实验组疼痛减轻率、睡眠质量改善率和饮食改善率均高于对照组，差异有统计学意义（P＜0.05），见表 2。

表 2 两组临床治疗效果对比[n(%)]

Table 2 Comparison of clinical efficacy between the two groups[n(%)]

Groups	n	Pain relief	Sleep quality improvement	Diet improvement
Experimental group	31	24(77.42)	22(70.97)	26(83.87)
Control group	31	15(48.39)	13(41.94)	15(48.39)
x^2		5.599	5.314	8.713
P		0.018	0.021	0.003

2.3 两组不良反应比较

患者不良反应主要有皮疹、瘙痒、皮肤干燥、恶心、腹泻、其他不良反应等，两组不良反应发生率比较均无统计学差异（P>0.05），见表 3。

表 3 两组患者不良反应比较[n(%)]

Table 3 Comparison of adverse reactions between the two groups[n(%)]

Groups	n	Erythra	Pruritus	Xerosis cutis	Nausea	Other
Experimental group	31	8(25.81)	4(12.90)	4(12.90)	2(6.45)	2(6.45)
Control group	31	9(29.03)	5(16.13)	5(16.13)	2(6.45)	3(9.68)
x^2		0.081	0.000	0.000	0.000	0.000
P		0.776	1.000	1.000	1.000	1.000

2.4 两组存活率比较

62 例 EGFR 阳性晚期 NSCLC 患者经过治疗后出院，在 1 年随访观察中，实验组有 3 例死亡，对照组有 9 例死亡。实验组存活率高于对照组，差异有统计学意义（P<0.05）。见表 4。

表 4 两组患者存活率比较

Table 4 Comparison of survival rates between the two groups

Groups	n	Death cases	Mortality rate(%)	Survival rate(%)
Experimental group	31	3	9.68	90.32
Control group	31	9	29.03	70.97
x^2	-	-	-	3.952
P	-	-	-	0.047

3 讨论

NSCLC 是临床上常见恶性肿瘤，发现时其分期较晚，失去了根治性手术的机会，目前针对 NSCLC 的主要治疗方式是放化疗，但是当前可供选择的细胞毒化学治疗药物的治疗效果有限[13-15]。因此，探究对 NSCLC 有效的化疗治疗方案具有重要的临床价值。吉非替尼片是一种选择性表皮生长因子受体酪氨酸激酶（TK）抑制剂，能选择性的抑制 EGFR，进而阻碍实体瘤的生长和转移，克服了细胞毒化学药物治疗的缺点，实体肿瘤病患者口服后耐受性良好，剂量限制性毒性为腹泻，且在 NSCLC 中疗效十分突出[16]。相关研究显示，通过阻断 EGFR 能够抑制肿瘤细胞生长，并降低中性成纤维细胞生长因子以及血管内皮生长因子的水平，进而对新生血管的生成起到抑制作用[17,18]。化疗药物可在细胞膜内选择性的抑制 EGFR 酪氨酸激酶，同时单克隆抗体可通过与其细胞外的配体结合，进而竞争性地阻断 EGFR 酪氨酸激酶，因此恶性肿瘤的发生、发展与 EGFR 信号通路密切相关[19]。EGFR 激活后可促进血管生成和细胞增殖，而大部分 NSCLC 患者存在 EGFR 表达或过表达，如何针对性的阻断 EGFR 信号传导，为靶向治疗 NSCLC 的关键所在。吉非替尼片可通过与三磷酸腺苷争夺催化区的结合位点，阻断 EGFR 信号传导，进而对肿瘤的发生、发展起到抑制作用[20]。

在肺癌的治疗中，中医的治疗思路主要是改善患者的临床症状以及生活质量，从而达到延长患者生命的目的。目前，有研究显示，中医素有的辅助治疗的功效，在治疗肺癌方面同样具有显著作用[21]。中药不但在减轻放、化疗的毒副作用、改善机体耐受性方面具有明显优势，而且其治疗方法更具有针对性[22,23]。艾迪注射液是一种具有抗肿瘤作用的中药制剂，主要由斑蝥、人参、刺五加、黄芪组成，能够抑制肿瘤血管新生，杀伤肿瘤细胞，同时艾迪注射液还有保护骨髓，调节免疫系统的作用，能改善患者生活质量，延长生存期[24]。其中斑蝥为君药，起到诱导肿瘤细胞的凋亡、调节免疫功能、促进骨髓造血干细胞成熟等作用；人参为臣药，具有扶正固本、补气养血等功效。现代药理证

明,人参能够增强人体的免疫功能,同时可抑制肿瘤细胞的发育,降低其发生浸润、转移的几率;黄芪为佐药,可调节人体的体液免疫和细胞免疫,增加 T 细胞的抗癌活性,增强对肿瘤细胞的杀伤力;刺五加为佐药,能增强患者身体耐受力,改善治疗过程中出现的毒副反应[25-27]。四种药物联合使用,起到了增强机体免疫力,杀伤肿瘤细胞的作用,因此艾迪注射液常用于治疗肺癌、肝癌等恶性肿瘤。

本研究在对 EGFR 阳性晚期 NSCLC 患者采用常规靶向药物吉非替尼片治疗的基础上联合应用艾迪注射液,观察患者治疗效果和不良反应情况。结果显示,实验组的有效率和疾病控制率明显提高,并且实验组疼痛减轻率、睡眠质量改善率和饮食改善率均高于对照组(P<0.05),实验组 1 年存活率高于对照组,差异有统计学意义(P<0.05),这说明两种药物联合治疗具有更好的临床疗效,能够更明显地改善患者的临床症状。尽管两组的不良反应差异没有统计学意义,但是联合用药的不良反应发生率稍低,说明吉非替尼片与艾迪注射液联合使用能稍微降低化疗的毒副反应, 为晚期 NSCLC 患者提供了新的治疗思路[28,29]。由于本研究样本例数较少,且具体作用机制尚无统一定论,缺乏相关的基础实验证实,因此还有待下一步的研究。但是研究中可以发现,吉非替尼片联合艾迪注射液治疗,只要遵循正确的用药规则,治疗方法是安全有效的,并且可行度很高[30]。

综上所述,艾迪注射液联合吉非替尼片治疗 EGFR 阳性晚期 NSCLC 的疗效确切,能够改善患者睡眠质量和饮食状况,减轻疼痛,用药安全性较好,有助于延长患者的短期生存,值得临床推广。

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