

doi: 10.13241/j.cnki.pmb.2017.17.033

鸦胆子油乳、艾迪注射液对非小细胞肺癌化疗效果的影响

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摘要 目的:分析鸦胆子油乳、艾迪注射液配合GP化疗治疗非小细胞肺癌的疗效及对免疫功能的影响。**方法:**以2010年1月至2016年3月宝鸡市解放军第三医院收治的非小细胞肺癌患者80例为研究对象,根据住院病历号顺序分为观察组和对照组,每组40例,对照组接受GP化疗方案,观察组接受GP化疗方案联合鸦胆子油乳、艾迪注射液治疗,两组均10天为一个周期,4个周期为一个疗程,均治疗1个疗程。比较两组的临床疗效、不良反应、T细胞亚群水平及生活质量评分。**结果:**观察组的总缓解率和疾病控制率分别为62.5%和92.5%,均显著高于对照组(47.5%和75.0%)(P<0.05);治疗后,两组的CD3⁺、CD4⁺、CD8⁺、CD4⁺/CD8⁺水平均较治疗前显著降低(P<0.05),观察组治疗后的CD3⁺、CD4⁺、CD8⁺水平明显高于对照组(P<0.05);两组治疗后的KPS评分均较治疗前升高,且观察组的KPS评分显著高于对照组(P<0.05);治疗期间,观察组的恶心呕吐、腹泻、白细胞计数减少、血小板减少、肝功能损害和肾功能损害的发生率均显著低于对照组(P<0.05);半年内,观察组的生存率(87.5%)显著高于对照组的生存率(77.5%)。**结论:**鸦胆子油乳、艾迪注射液配合GP化疗治疗非小细胞肺癌的疗效显著,不良反应发生率低,提高半年生存率,而且可降低化疗对T细胞亚群水平的影响,并降低患者血清VEGF水平。

关键词:非小细胞肺癌;鸦胆子油乳;艾迪注射液;GP化疗方案

中图分类号:R734.2 **文献标识码:**A **文章编号:**1673-6273(2017)17-3331-04

Clinical Effect of Brucea Javanica Emulsion Oil, Aidi-injection with GP Chemotherapy in Patients with Non Small Cell Lung Cancer

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ABSTRACT Objective: To investigate the clinical effect of brucea javanica emulsion oil, Aidi-injection with GP chemotherapy in patients with non small cell lung cancer and the influence on immune function. **Methods:** 80 cases of patients with non small cell lung cancer in our hospital from January 2010 to March 2016 were divided into observation group and control group, 40 cases in each group. The patients in the control group were treated with GP chemotherapy, and the patients in the observation group were treated with brucea javanica emulsion oil, Aidi-injection with GP chemotherapy. 10 days for a cycle, four cycles for a period of treatment, treatment time of both groups were 1 course of treatment. The clinical effect, adverse effects and T cell subgroup level were compared between two groups. **Results:** The overall response rate and disease control rates of the observation group were significantly higher than those of the control group (P<0.05); After treatment, the levels of CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺, VEGF of the two groups were significantly lower than before treatment (P<0.05), and these indexes were significantly higher in the observation group than those of the control group (P<0.05); After treatment, the KPS score of two groups was significantly higher than before treatment (P<0.05), and it was significantly higher in the observation group than that of the control group (P<0.05); the rate of adverse reactions of the observation group during therapy were significantly lower than those of the control group (P<0.05); half-year survival rate of the observation group were significantly higher than that of the control group (P<0.05). **Conclusions:** Brucea javanica emulsion oil, Aidi-injection with GP chemotherapy can effectively improve the clinical effect, reduce the adverse reactions, and can alleviate the effects of chemotherapy on T cell subgroup level, and reduce the level of VEGF.

Key words: Non small cell lung cancer; Brucea javanica emulsion oil; Aidi-injection; GP chemotherapy

Chinese Library Classification(CLC): R734.2 **Document code:** A

Article ID: 1673-6273(2017)17-3331-04

前言

非小细胞肺癌是肺癌中最常见的组织学类型,约占肺癌的

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(收稿日期:2016-09-22 接受日期:2016-10-21)

80%-85%,且发病率逐年升高,已经成为我国乃至全球致死率最高的肿瘤^[1]。非小细胞肺癌的细胞生长分裂速度较慢,确诊时多已处于中晚期,失去了手术的最佳条件,一般只能采取化疗姑息治疗^[2]。但化疗毒副反应较大,部分患者无法耐受而中断治疗,同时化疗患者免疫功能普遍低下,增加了潜在感染风险,最终影响化疗效果^[3]。艾迪注射液和鸦胆子油乳为中药制剂,能够

靶向杀灭肿瘤细胞,且具有保护机体免疫功能的作用^[4,5]。何敏^[6]等研究显示,鸦胆子油乳、艾迪注射液配合GP化疗治疗非小细胞肺癌的疗效显著且可降低患者血清白细胞介素、肿瘤坏死因子等炎症因子水平。本研究拟分析,鸦胆子油乳、艾迪注射液联配合GP化疗治疗非小细胞肺癌的疗效、不良反应及对患者T细胞亚群(CD3⁺、CD4⁺、CD8⁺、CD4^{+/CD8⁺)及血管内皮生长因子(VEGF)水平的影响。}

1 资料与方法

1.1 一般资料

2010年1月至2016年3月宝鸡市解放军第三医院收治非小细胞肺癌患者80例,均经病理组织学确诊,病灶可客观测量,预计生存期在12周以上,所有患者均无放疗和化疗史,治疗前血常规、肝肾功能、心电图等均正常,知情同意本研究。将80例患者根据住院病历号顺序分为观察组和对照组,每组40例,其中观察组中男27例,女13例;年龄55~79岁,平均年龄52.2±8.5岁;TNM分期III期19例,IV期21例;腺癌29例,鳞癌6例,鳞腺混合癌5例;对照组中男28例,女12例;年龄55~78岁,平均年龄52.8±8.1岁;TNM分期III期20例,IV期20例;腺癌28例,鳞癌7例,鳞腺混合癌5例。两组患者的一般资料差异无统计学意义($P<0.05$)。

1.2 方法

对照组接受GP化疗方案:治疗第1d和第8静脉滴注吉西他滨(南京正大天晴制药有限公司,国药准字H20093403,规格:0.2g)1.0g/m²,第2d至第4d静脉滴注顺铂(江苏豪森药业集团有限公司,国药准字H20040812,规格:2mL:10mg)30g/m²。

观察组接受GP化疗方案联合鸦胆子油乳、艾迪注射液治疗:GP化疗方案同对照组,鸦胆子油乳:于化疗开始当天加用鸦胆子油乳(广州白云山明兴制药有限公司,国药准字Z44021325,规格:10mL)和艾迪注射液(贵州益佰制药股份有限公司,国药准字Z52020236,规格:10mL),20mL鸦胆子油乳加入250mL生理盐水中静脉滴注,每天1次,50mL艾迪注

射液溶于250mL 5%葡萄糖溶液中静脉滴注,每天1次。

两组均10天为一个周期,4个周期为一个疗程,两组均治疗1个疗程。

1.3 观察指标

(1)于化疗前和化疗结束后次日清晨抽取患者空腹静脉血5mL,采用流式细胞仪(艾森生物(杭州)有限公司,型号:NovoCyte D1041)检测患者血中CD3⁺、CD4⁺、CD8⁺、CD4^{+/CD8⁺的数量,采用曼联免疫吸附法检测患者血清VEGF水平,所有操作严格按照试剂盒操作说明进行,试剂盒购自南京建成生物工程研究所;(2)根据WHO的抗癌药物不良反应分度标准统计治疗期间两组出现的I~IV度不良反应发生情况;(3)采用Karnofsky功能状态评分标准(KPS)评价治疗前后患者生活质量变化情况,满分100分,得分越高,表示健康状况越好;(4)电话随访半年,获得患者半年的生存率。}

1.4 疗效标准

两组患者化疗1个疗程后采用WHO的实体瘤评价标准评价疗效:完全缓解(CR):病灶消失且无新病灶出现,肿瘤标志物水平正常,维持至少4周;部分缓解(PR):无新病灶出现,靶病灶的最大径与最大垂直径乘积减小大于50%及以上,维持至少4周;无变化(SD):无,靶病灶的最大径与最大垂直径乘积减少小于50%或增加小于25%;病情进展(PD):有新病灶出现,或靶病灶的最大径与最大垂直径乘积增加25%及以上^[6]。总缓解率=CR+PR,疾病控制率=CR+PR+SD。

1.5 统计学方法

采用SPSS17.0进行统计分析,计数资料以%表示,采用卡方检验,计量资料以均值±标准差表示,采用t检验,以 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 两组临床疗效比较

观察组的总缓解率和疾病控制率分别为62.5%和92.5%,均显著高于对照组(47.5%和75.0%)($P<0.05$)。

表1 两组临床疗效比较

Table 1 Comparison of clinical effects in two groups(n,%)

Groups	Cases	CR	PR	SD	PD	Overall response rate(%)	Disease Control Rate(%)
Observation group	40	15	10	12	3	62.5 ^a	92.5 ^a
Control group	40	10	9	11	10	47.5	75.0

Note: Compared with control group.^a $P<0.05$.

2.2 治疗前后两组T细胞亚群及VEGF水平比较

两组治疗前的T细胞亚群及VEGF水平比较,差异均无统计学意义($P<0.05$);治疗后,两组的CD3⁺、CD4⁺、CD8⁺、CD4^{+/CD8⁺水平及VEGF水平均较治疗前显著降低($P<0.05$),观察组的CD3⁺、CD4⁺、CD8⁺明显高于对照组($P<0.05$),VEGF水平明显低于对照组($P<0.05$)。}

2.3 两组治疗前后KPS评分比较

两组治疗前的KPS评分比较,差异无统计学意义($P<0.05$);治疗后,两组的KPS评分均较治疗前升高,且观察组明显高于对照组($P<0.05$)。

2.4 两组不良反应发生情况比较

治疗期间,观察组的恶心呕吐、腹泻、白细胞计数减少、血小板减少、肝功能损害和肾功能损害的发生率均显著低于对照组($P<0.05$)。

2.5 两组半年生存率比较

半年内,观察组的生存率为87.5%(35/40),对照组的生存率为77.5%(31/40),两组半年生存率比较,差异有统计学意义($P<0.05$)。

3 讨论

表 2 两组治疗前后 T 细胞亚群水平变化($\bar{x} \pm s$)
Table 2 Comparison of T cell subgroup level in two groups($\bar{x} \pm s$)

Groups	Cases		CD3 ⁺ (%)	CD4 ⁺ (%)	CD8 ⁺ (%)	CD4 ⁺ /CD8 ⁺	VEGF(ng/L)
Observation group	40	Before treatment	58.25± 2.68	39.81± 2.25	32.97± 2.16	1.21± 0.23	261.19± 32.51
		After treatment	53.25± 2.15 ^①	32.56± 2.09 ^①	30.02± 2.11 ^①	1.08± 0.19 ^①	110.69± 26.55 ^①
Control group	40	Before treatment	57.89± 2.37	39.17± 2.22	32.77± 2.29	1.19± 0.21	263.81± 33.71
		After treatment	41.03± 1.88 ^②	28.45± 2.11 ^②	27.65± 2.17 ^②	1.03± 0.15 ^②	191.33± 29.68 ^②

Note: Compared with before treatment ^① P<0.05; Compared with control group, ^② P<0.05.

表 3 两组生活质量比较
Table 3 Comparison of KPS scores between two groups

Groups	Cases	KPS scores	
		Before treatment	After treatment
Observation group	40	72.56± 3.96	86.91± 7.44 ^①
Control group	40	71.33± 3.88	77.62± 5.77 ^②

Note: Compared with before treatment, ^① P<0.05; Compared with control group, ^② P<0.05.

表 4 两组治疗期间不良反应发生情况比较
Table 4 Comparison of incidence of adverse reactions between two groups

Groups	Cases	Nausea and vomiting	Diarrhea	Leukocytopenia	Thrombocytopenia	Liver function damage	Renal function lesion
Observation group	40	I and II	9	5	8	3	1
		III and IV	4	3	11	5	2
		Total incidence	13(32.5) ^①	8(20.0) ^①	19(47.5) ^①	8(20.0) ^①	3(7.5) ^①
Control group	40	I and II	16	5	10	13	3
		III and IV	8	9	11	4	8
		Total incidence	24(60.0)	14(35.0)	21(52.5)	17(42.5)	11(27.5)

Note: Compared with control group, ^① P<0.05.

非小细胞肺癌是临床常见的肺癌类型,以铂类药物为基础的GP化疗方案是目前临床治疗中晚期非小细胞肺癌的一线化疗方案,可有效控制病灶扩散,改善临床症状,提高患者的生活质量,但随着化疗时间的延长,以胃肠道反应、骨髓抑制、肝肾功能损害为主的不良反应发生率逐渐升高,严重影响患者的机体功能及化疗效果,部分患者甚至不能耐受而终止治疗^[7,8]。近年来,中药辅助GP化疗方案治疗非小细胞肺癌取得了较显著的治疗效果,化疗在祖国医学中归属“热毒、攻伐”范畴,其引起的不良反应主要因耗气伤阴、损伤气血、伤及脾胃肝肾等脏腑所致^[9]。因此对于化疗引起的不良反应,中医以清热解毒、调养脏腑为主^[10]。

鸦胆子油乳为苦木科植物鸦胆子的成熟种子中提取的脂肪油经乳化作用制成的水包油型乳剂,主要抗癌活性成分为油酸和亚油酸^[11]。鸦胆子油乳发挥抗肿瘤作用的机制主要是:抑制拓扑异构酶的活性,从而抑制肿瘤细胞DNA的合成,杀伤和抑制癌细胞,同时鸦胆子油乳的细小油乳颗粒与肿瘤细胞有特异性的亲和力,可长时间粘附在肿瘤细胞周围,从而有利于抗肿瘤成分渗入肿瘤细胞内,减少对正常组织细胞的伤害,降低不良反应^[12]。鸦胆子油乳还可激活机体免疫系统,恢复机体免疫力^[13]。艾迪注射液是由斑蝥、人参、黄芪和刺五加等中药制剂的中药注射剂,具有清热解毒、散结消淤的功效^[14]。现代药理研究显示,艾迪注射液通过细胞周期阻滞和诱导凋亡抑制肿瘤细

胞增殖,通过抑制细胞生长因子的表达抑制肿瘤血管生成,通过提高患者机体CD细胞、NK细胞、免疫球蛋白水平,提高机体的免疫功能,抑制肿瘤细胞活性^[15,16]。何敏^[6]等研究显示,鸦胆子油乳、艾迪注射液联合GP化疗方案可显著提高非小细胞肺癌患者的治疗效果。本研究结果同样显示,鸦胆子油乳、艾迪注射液和GP化疗联合应用的观察组总缓解率和疾病控制率均显著高于单用GP方案的对照组(P<0.05);治疗后,两组的KPS评分均较治疗前升高,且观察组显著高于对照组(P<0.05)。提示,联合用药可显著改善提高临床疗效,提高生活质量,原因可能为联合用药通过不同的作用机制发挥协同抗癌作用。

免疫功能受损是肿瘤患者化疗中的常见现象,不仅影响临床疗效,而且威胁患者的生命安全^[17,18]。椰慧楠^[19]等研究显示,与单用GP化疗方案相比,鸦胆子油乳联合GP化疗方案治疗非小细胞肺癌后患者的CD3⁺、CD4⁺、CD8⁺、CD4⁺/CD8⁺水平及NK水平明显较高。张宏伟^[20]等研究显示,与单用GP化疗方案相比,艾迪注射液联合GP化疗方案治疗非小细胞肺癌均可有效升高患者CD4⁺、CD4⁺/CD8⁺水平。本研究中,治疗后,两组的CD3⁺、CD4⁺、CD8⁺、CD4⁺/CD8⁺水平均较治疗前显著降低(P<0.05),但观察组的CD3⁺、CD4⁺、CD8⁺水平明显高于对照组(P<0.05)。而何敏^[6]等研究显示,鸦胆子油乳、艾迪注射液联合GP化疗方案可显著调节非小细胞肺癌患者体内白介素-6、白介素-10、肿瘤坏死因子等的水平,结合本研究结果与何敏等的

研究结果,提示,鸦胆子油乳、艾迪注射液联合 GP 化疗方案治疗非小细胞肺癌可有效恢复患者化疗中的免疫功能。本研究与何敏等的研究不同之处还在于对于患者血清的 VEGF 水平进行了观察,VEGF 通过与相应受体结合诱导新生血管的生成,患者血清 VEGF 水平的高低反应了肿瘤细胞的活性,本研究结果显示,观察组和对照组治疗后的 VEGF 水平均较治疗前降低,且观察组显著低于对照组,本研究中对照组患者治疗前后血清 VEGF 水平降低幅度与相关研究结果^[21]基本一致,但观察组治疗前后血清 VEGF 水平降低幅度较高,提示鸦胆子油乳、艾迪注射液联合提高 GP 化疗方案治疗非小细胞肺癌临床疗效的作用机制可能与降低 VEGF 水平有关。本研究还显示,治疗期间,观察组的恶心呕吐、腹泻、白细胞计数减少、血小板减少、肝功能损害和肾功能损害的发生率均显著低于对照组,观察组的半年生存率显著高于对照组($P<0.05$)。提示,联合用药可显著减低患者的胃肠道反应、骨髓抑制等不良反应发生率,提高生存率。但由于本研究样本量少,研究未对鸦胆子油乳、艾迪注射液联合 GP 化疗方案与鸦胆子油乳联合 GP 化疗或艾迪注射液联合 GP 化疗治疗非小细胞肺癌之间的差异进行比较,还有待进一步研究。

综上所述,鸦胆子油乳、艾迪注射液配合 GP 化疗治疗非小细胞肺癌的疗效显著,不良反应发生率低,提高半年生存率,而且可降低化疗对 T 细胞亚群的影响,并较低患者血清 VEGF 水平。

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