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多柔比星脂质体单药和联合洛铂方案治疗复发卵巢癌的临床研究 *

乔谷媛 陈良凤 马园园 张 博 王 建△

（第四军医大学西京医院妇产科 陕西 西安 710032）

摘要 目的：评价盐酸多柔比星脂质体单药(PLD)与盐酸多柔比星脂质体联合洛铂治疗复发性卵巢癌的安全性和临床疗效。**方法：**收集 2012 年 4 月至 2015 年 10 月我科收治的 31 例复发晚期上皮性卵巢癌患者，根据患者是否存在铂类耐药分为多柔比星组(单药组)15 例及多柔比星＋洛铂组(对照组)16 例。单药组给盐酸多柔比星脂质体 50 mg/m^2，静滴；对照组给盐酸多柔比星脂质体 20-30 mg/m^2，洛铂 30-50 mg/m^2，静脉滴注，两组每 21-28 天重复一次，观察和比较两组的临床疗效和毒性反应的发生情况。结果：所有患者完成 3-8 周期，客观有效率(ORR)为 38.7 %。单药组为 33.3 %，对照组为占 43.8 %，两组 ORR 比较差异无统计学意义(P=0.411)。单药组骨髓抑制的毒副作用较对照组发生率显著升高高(P=0.019)，两组其他毒副反应的发生情况比较差异无统计学意义(P>0.05)。单药组和对照组中位生存时间(MST)分别为 10 个月(95 % CI：1.242-18.758)、18 个月(95 % CI：8.261-27.739)，中位无进展生存期(PFS)分别为 7 个月(95%CI：2.210-13.797)、13 个月(95 %CI：4.368-21.632)，两组 MST、PFS 比较差异均无统计学意义(P>0.277)。**结论：**聚乙二醇脂质体阿霉素单体或聚乙二醇脂质体阿霉素联合洛铂治疗复发性卵巢癌的疗效相当，而聚乙二醇脂质体阿霉素单体的安全性更高。

关键词：卵巢癌；化疗；盐酸多柔比星脂质体；洛铂；毒性反应

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A Clinical Study on the Efficacy of Pegylated Liposomal Doxorubicin or Combination of Liposomes and Lobaplatin in the Treatment of Recurrent Ovarian Cancer*

QIAO Gu-yuan, CHEN Liang-feng, MA Yuan-yuan, ZHANG Bo, WANG Jian△

(Department of obstetrics and gynecology, Xiking fourth military medical university hospital, Xi'an, Shaanxi, 710032, China)

ABSTRACT Qbjective: To evaluate the safety and clinical efficacy of pegylated liposomal doxorubicin (PLD) and lobaplatin in the treatment of patients with recurrent ovarian cancer. **Methods:** According to platinum resistance level, 31 cases of patients with recurrent advance epithelial ovarian cancer admitted from April 2012 to October 2015 in our department were divided into two groups: 15 patients in the doxorubicin group (single drug group) and 16 patients in the doxorubicin combined with lobaplatin group (control group). The patients in single drug group were given 50 mg/m^2 pegylated liposomal doxorubicin by intravenous drip. The patients in control group were given 20-30 mg/m^2 pegylated liposomal doxorubicin and 30-50 mg/m^2 lobaplatin by intravenous drip. All patients were repeated every 21-28 days. Besides, the clinical efficacy and toxicity of two groups were observed and compared. **Results:** After 3-8 cycles treatment, the total objective response rate (ORR) was 33.3%, which were 38.7 % and 43.8 % in the single drug group and control group respectively. There was no statistically significant difference in the ORR between two groups (P=0.411). The incidence of myelosuppression in single drug group was significantly higher than that of the control group (P=0.019), and there was no statistically significant difference in the incidence of other adverse reactions between two groups (P>0.05). The median survival time (MST) of single drug group and the control group were 10 months (95% CI: 1.242-18.758), 18 months (95% CI: 8.261-27.739), and the median progression free surial (PFS) were 7 months (95% CI: 2.210-13.797), 13 months (95% CI: 4.368-21.632) respectively. The MST, PFS had no statistically significance difference between the two groups (P>0.277). **Conclusions:** Pegylated Liposomal Azithromycin had equivalent efficacy to combination of Liposomes with Lobaplatin in the treatment of recurrent ovarian cancer, while the safety of Pegylated Liposomal Azithromycin was higher.

Key words: Ovarian cancer; Chemotherapy; Pegylated liposomal doxorubicin; Lobaplatin; Toxic effects

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前言

卵巢恶性肿瘤是女性生殖系统常见的三大恶性肿瘤之一[1]，

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作者简介：乔谷媛(1977-)，女，硕士研究生，主治医师，研究方向：妇科肿瘤，围产期医学，电话：13720602229，E-mail: qiaoguyua@163.com

△ 通讯作者：王建(1962-)，男，硕士，主任医师、教授，研究方向：妇科肿瘤，子宫内膜异位症，电话：13891851099

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尽管大多数卵巢癌患者能在手术和一线化疗后达到完全缓解，由于原发性与继发性耐药，约 50%-70%的患者在 2 年内复发，复发后选择有效而毒性低的药物显得非常重要。为了保证患者接受到科学安全有效的治疗，在关注药物的治疗效果和不良反应的同时更应该关注其生存质量评分 [2,3]。2015 版卵巢癌 NCCN 指南推荐对铂类耐药可给予脂质体阿霉素单药或联合方案进行治疗。盐酸多柔比星脂质体(聚乙二醇脂质体阿霉素，PLD)属于蒽环类抗肿瘤药物，抗瘤谱广。洛铂属于第三代全新铂类抗癌类药物，实验数据证实对包括卵巢癌在内的多种肿瘤治疗效果显著[4,5]。因此，本研究主要观察和比较 PLD 单药与 PLD 联合洛铂的治疗复发性卵巢癌的临床效果及安全性，现报道如下：

1 资料与方法

1.1 一般资料

根据卵巢癌国际 FIGO 分期方法，选取 2012 年 4 月 -2015 年 10 月收治的经手术及病理确诊的Ⅲ期卵巢癌患者，年龄 25-65 岁，平均年龄 45± 3.5 岁。纳入标准：治疗后复发或疾病进展临床指标中，出现下列 2 项：① CA125 升高≥ 100 U/mL；② 体检或影像学资料发现肿块，有明确的可测量病灶作为评价疗效；③ 不明原因的肠梗阻；④ 甚至出现胸腹水，即为复发或疾病进展。化疗前对病人全身状况进行评价，有足够的肝肾及骨髓功能，心脏功能良好(左室射血分数≥ 50 %)，体能状态评分 ECOG≤ 2；无明显的化疗禁忌症。病理组织学类型：浆液性癌 21 例，黏液性癌 7 例，透明细胞癌 2 例，鳞状细胞肿瘤 1 例。根据患者复发时间分为铂类敏感型复发(铂类治疗后获得完全缓解，停止治疗后至复发间隔 >6 月)及铂类耐药型复发(铂类治疗后未获得完全缓解或完全缓解后停止化疗至复发间隔时间≤ 6 月)。

1.2 治疗方法

所有患者均接受卵巢癌细胞减灭术配合紫杉醇、铂类药物联合化疗治疗方案。所有患者根据患者病情，是否存在铂类耐药，分为单药组和对照组，单药组给予 PLD50 mg/m^2+5 %葡萄糖溶液 500 mL，静脉滴注，1 d 给药；对照组接受 PLD+ 洛铂的治疗方案：PLD 20-30 mg/m^2+5 %葡萄糖溶液，洛铂 30-50 mg/m^2+5 %葡萄糖溶液 500 mL，静脉滴注，1 d 给药。化疗时常规给予预防止吐，保护胃粘膜，抗过敏的药物行预处理。21-28 d 为 1 周期。

每周期查血常规、生化全套、心电图，CAl25 及影像学检查，评价不良反应，疗效评价时间为每 2 个周期。根据其疗效判定患者是否需要继续化疗。化疗疗程结束后 PET-CT 检测评估化疗结果。针对在治疗的过程中出现白细胞、血小板减少的患者，则在每组药物治疗的基础上予以患者粒细胞集落刺激因子或粒细胞 - 巨噬细胞集落刺激因子辅助治疗。如若出现Ⅲ-Ⅳ度的毒性反应(WHO 定义)或出现与剂量有关的手足综合征(痛性红肿，掉皮，间断性水疱)时，则可酌情延长治疗的时间间隔和(或)减少剂量。

1.3 疗效评价标准

根据实体瘤客观疗效评价标准(Response Evaluation Criteria in Solid Tumors，RECIST)判定其疗效，按照患者的病情好转程度分为完全缓解 (Complete response，CR)、部分缓解(Partial response，PR)、稳定(Stable disease，SD)和进展(Progressive disease，PD)。以 CR+PR 计算客观有效率(Objective response rate，ORR)，无进展生存期(Progression free survival，PFS)是指从诊断至患者疾病 PD 时间。此外，针对服药后的毒副作用进行考察，根据 WHO(1981 年)抗癌药物急性毒性表现进行分级，其中Ⅲ-Ⅳ级视为严重不良事件。分别以 ORR，PFS 及化疗的毒副作用作为评价指标。

1.4 统计学分析

采用统计学软件 SPSS22.0 分析实验结果，计量资料以均数± 标准差($\bar{x}$± s)表示。计数资料采用 fisher 确切概率法，生存分析用 Kaplan-Meier 法，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

所有接受治疗的患者治疗时间均在 3 个周期以上。时间截止到 2015 年 10 月，其中有 3 例患者失访，剩余 28 例患者对疗效进行评价，随访率达 90.3 %。

总体上，ORR 为 38.7 %，CR1 例(3.2 %)，PR11 例(35.5 %)，SD14 例 (45.2 %)，PD5 例 (16.1 %)。其中，单药组 ORR 为 33.3%，对照组 ORR 为 43.8 %，两组 ORR 比较差异无统计学意义(P=0.411)。

表 1 两组临床疗效的比较

Table 1 Comparison of clinical efficacy between two groups

Group	n	CR	PR	SD	PD	ORR(%)
Single drug group	15	0	5	8	2	33.3
Combined drug group	16	1	6	6	3	43.8
Total	31	1	11	14	5	38.7

2.2 两组不良反应发生情况的比较

针对接受化疗治疗的患者所出现的药物不良反应进行记录和分析，临床数据结果显示主要存在消化道毒性、血液学毒性，偶有轻度肝功能损害、口腔皮肤红斑等不良反应[6]。因用药前给予预处理，未见过敏反应发生。治疗过程中所出现的毒副反应在对症处理后均有改善，且无死亡病例。31 例患者中，3 例患者出现Ⅳ度骨髓抑制，其中 PLD 单药化疗 1 例，联合化疗组(对照组)2 例。在化疗过程中，不同程度的血小板下降的患者 10 例(32.26%)、白细胞下降 25 例(80.65%)和红细胞下降 17 例(54.84%)。非血液学方面：临床常伴有食欲不振、恶心呕吐、乏力、便秘及皮肤异常感觉等不良反应。其中，Ⅱ-Ⅲ级呕吐(暂时性呕吐及需要治疗的呕吐)的患者 23 例(74.19%)。所有患者均

未出现严重的心肝肾功能损害、手足综合症及心脏毒性等毒副反应。患者接受治疗的时间内，未有患者因不良反应而停药。结果详见表 2。

表 2 31 例患者的主要化疗相关毒副反应的发生情况

Table 2 The incidence of main chemotherapy toxic side effects of 31 cases of patients

Toxic side effects	Ⅰ	Ⅱ	Ⅲ	Ⅳ	Total
White blood cells descend	11	5	6	3	25(80.65%)
Anemia	8	5	2	0	17(54.84%)
Platelet descend	3	5	2	0	10(32.26%)
Nausea and vomiting	7	11	5	0	23(74.19%)
Rise of serum transaminase	3	0	0	0	3(9.68%)
Nise of creatinine	2	0	0	0	2(6.45%)

患者多柔比星脂质体累最高累积剂量 240 mg/m^2，除个别患者用药期间出现窦性心动过速，心电图提升轻度房室传导阻滞外，在用药过程及化疗完成后患者心肌酶谱无异常，超声心动检查提示心功能正常，未影响后续用药。两组患者均有脱发，轻度皮肤异常感觉，患者的皮肤异常感觉包括皮肤色素沉着，指端麻木感。单药组骨髓抑制的毒副作用较对照组发生率高(P=0.019)，而两组其他毒副反应的发生情况比较差异无统计学意义(P>0.05)。见表 3。

表 3 两组患者化疗相关毒副反应发生情况的比较

Table 3 Comparison of the incidence of main chemotherapy toxic side effects between two groups

Group	Gastrointestinal symptoms	ECG responses	Liver function	Kidney function	Bone marrow suppression(Ⅲ,Ⅳ)
Single drug group	12	9	2	1	6
Control group	11	5	1	1	3
P	0.328	0.314	0.475	00.742	0.019

2.3 两组生存情况随访

至 2015 年 10 月 31 日共 42 个月，采用 Kaplan-Meier 法计算并得出总生存曲线和无疾病进展生存曲线，结果见图 1。患者接受化疗后其总生存时间为 3-42 个月，单药组组和对照组中位生存时间(MST)分别为 10 个月(95 % CI：1.242-18.758)、18 个月(95 % CI：8.261-27.739)，两组中位生存时间比较差异无统计学意义(P=0.211)。单药组无进展生存期(PFS)2-38 个月，中位 PFS7 个月 (95%CI：2.210-13.797)；对照组 3-42 个月，中位 PFS13 个月(95 %CI：4.368-21.632)。两组中位生存时间比较差异无统计学意义(P=0.277)。

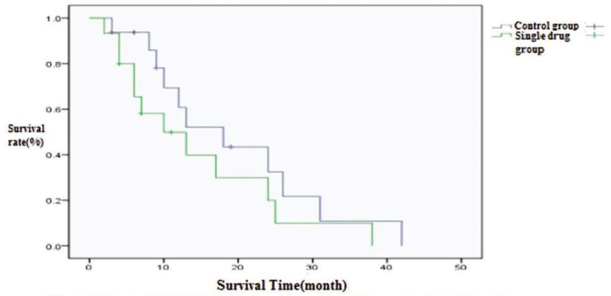

Figure 1.Comparison of survival curves of two chemotherapy regimens in patients with relapsed platinum resistant ovarian cancer

3 讨论

卵巢癌是女性癌症的第五大死因[7]，国际上通用的治疗策略是全面的分期手术[8,9]和(或)肿瘤细胞减灭术[10]，减少肿瘤负荷，术后给予规范、足量的化疗[11]。尽管大多数卵巢癌患者能在手术和一线化疗后达到完全缓解，但治疗过程中的耐药和复发的问题仍困扰着患者及临床医生[12]。对于复发性或铂类耐药的卵巢癌患者而言，选择有效而毒性低的药物显得非常重要，多选用未接触过的单药或作用机制不同的药物进行联合给药[13]。

目前，对于铂耐药型复发性患者，推荐首选非铂类单药化疗，延长无铂间期。PLD 作为改进的蒽环霉素类药物因半衰期长、清除率低、血浆药物浓度高，克服耐药性，增加药物被癌细胞摄取，被认为是有效的治疗卵巢癌的二线药物[14,16-18]。据统计，应用 PLD 治疗妇科肿瘤 ORR 为 9.5 %-38 %[15]。本研究中，31 例复发卵巢癌患者肿瘤应用脂质体阿霉素单药及联合应用洛铂化疗后的总体的 ORR 为 38.7 %。铂类耐药组单独应用 PLD 的 ORR 为 33.3%，其中 CR 1 例(3.2 %)，PR11 例(35.5 %)。2014 年，三期临床研究表明铂类合并 PLD 在治疗铂类敏感性卵巢癌疗效上与传统上紫杉醇铂类联合方案间无明显差异[19]。洛铂属烷化剂，是第 3 代铂类抗癌药[20]，即 1,2- 二氨基 - 环丁烷乳酸合铂，是通过阻碍 DNA 复制发挥抗肿瘤作用，其可诱导顺铂耐药卵巢癌细胞凋亡[4]。国外 II 期研究以单药治疗复发性卵巢癌有效率 5/21 (24%)[21]。本研究中，PLD 联合洛铂的 ORR 为 43.8 %。其中，CR1 例，PR 共 6 例，与 PLD 单药比较差异无统计学意义。临床上对患者的用药选择上可以根据患者病情酌情应用二代或三代铂类药物。

有研究表明相对于其他组织而言，阿霉素类化合物对心肌的亲和力最强[23]，且可设计实现盐酸多柔比星与甲氧基聚乙二醇表面的结合，对其进行工艺改造包封于脂质体内，从而避免单核巨噬细胞(MPS)的识别与清除，最终达到提高其半衰期的

目的,增加抗肿瘤作用。本研究应用多柔比星脂质体最高累积剂量达 240 mg/m^2,除个别患者出现轻度房室传导阻滞外,心肌酶谱、左室射血分数等均无异常。大量研究表明脂质体技术对克服阿霉素心脏毒性尤为有效[21]。多中心的研究表明脂质体阿霉素联合卡铂治疗铂类敏感复发卵巢癌疗效显著,大幅度降低过敏反应、脱发、中性粒细胞减少和神经毒性等不良反应[16]。对于血液系统毒副反应而言,大多数患者都属于Ⅰ-Ⅱ度反应,其余Ⅲ-Ⅳ度严重患者的血红蛋白下降、白细胞下降及血小板下降分别为 6.5 %(2/31)、29.0 %(9/31)和 6.5 %(2/31),其发生率较低。据文献报道,一项Ⅱ期临床项目的 PLD 剂量为 45 mg/m^2,随着给药时间的延长,白细胞减少的发生率大幅度下降,而疗效无显著性差异,提示其不良反应发生率与治疗间隔、剂量存在相关性[24]。而单药组骨髓抑制率较对照组高可能与 PLD 药物剂量相关。另外,在对照组中,患者血小板减少较单药组明显增多,可能和洛铂类药物的副作用有关。在本研究中,仅一例患者在化疗第 8 疗程时出现Ⅳ度骨髓抑制,通过输血、升白细胞、支持对症治疗好转。非血液系统毒副反应主要以脱发、恶心呕吐、乏力或皮肤感觉异常为多发,程度较轻,经对症处理均可缓解,化疗间无治疗相关死亡。

Salah-Eldin Mam 等发现 38 例卵巢癌患者经紫杉类和铂类一线治疗后,属于 " 进展 " 范围内的患者经再次使用奥沙利铂和脂质体阿霉素进行联合化疗后,总 ORR 为 31.5 %,临床获益率 73.7 %,中位肿瘤进展时间(TTP)和总生存分别是 5.5 个月、10 个月[25],肯定了脂质体阿霉素单药及联合应用脂质体阿霉素及洛铂化疗对复发性卵巢肿瘤的治疗疗效。也有研究应用 PLD 联合紫杉醇药物非铂类药物治疗复发性卵巢癌,效果得到肯定[26]。有作者对 PLD 联合卡铂临床疗效评价中发现相比较一线传统化疗方案,PLD 和卡铂联合治疗卵巢癌患者的总生存率无差别,但无进展生存期明显提高。二本研究中,两组患者 PFS 单药组 2-38 个月,中位 PFS 7 个月,而对照组 3-42 个月,中位 PFS 13 个月,两组比较差异无统计学意义(P=0.21)。本研究中纳入患者至少完成 3 周期以上的化疗。由于副作用较低,患者有较好的耐受性,提示上述方案可作为治疗复发性卵巢癌较好的选择。由此可见,聚乙二醇脂质体阿霉素单体或聚乙二醇脂质体阿霉素联合洛铂治疗复发性卵巢癌的疗效相当,而聚乙二醇脂质体阿霉素单体的安全性更高。由于研究仅局限在卵巢癌复发晚期病例,还有待于在后面的临床工作中积累病例,扩大样本量,以及对患者追踪进一步深入研究。

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