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研究简报

芳基三氮烯甲氧嘧啶对小鼠 Lewis 肺癌转移的预防作用及形态学观察*

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前文报道，芳基三氮烯甲氧嘧啶(ATMP)可选择性地抑制 Lewis 肺癌的自发性转移，其作用环节可能是抑制原发瘤细胞的脱落[1]。为了探讨 ATMP 抗转移的实际应用价值及作用机理，本文以 Lewis 肺癌为模型，模拟临床手术加化疗的治疗方案进行实验研究，并观察了ATMP对原发瘤的形态学改变以及对 LA-795 肺腺癌自发性转移的作用。

ATMP 由本所合成室提供，配制时以 1%吐温助溶；环磷酰胺(CY)系上海第十二制药厂产品，以生理盐水新鲜配制应用。C 57 BL/6，T-739 近交系雌性小鼠，体重 17～22 g。Lewis肺癌、LA-795 肺腺癌瘤源由本所提供。

截肢加药物治疗实验 小鼠右后肢肌内接种 Lewis 肺癌细胞 8×10^5/只，接种后 24 h 给药。除对照组外，两次实验的其余各组分别于接种后第 9、11 天截肢切除原发瘤(以下简称截肢)。截肢过程如下：乙醚麻醉、消毒，环形剪开患肢上方皮肤，结扎股动脉及其周围循环血管，在尽量远离肿瘤部位的上方截肢，此过程中避免肿瘤组织与正常组织接触以及肿瘤组织的血液流到正常组织。截肢后比较术前给药组和单纯截肢组的肢重，计算抑瘤率。肺转移评定方法及抗 LA-795肺腺癌自发性转移实验见文献[1]。

对Lewis肺癌原发瘤的组织学和电镜观察 将 20 只小鼠随机平均分成两组，右腋皮下接种 Lewis 肺癌，给药组于接种后第二天起 ip ATMP 20 mg/kg×10 d,对照组给等量溶剂，停药后第二天取瘤作组织学及透射电镜观察。

结果表明：第 9 天截肢实验组，ATMP 术前给药对原发瘤的生长无抑制作用，但能明显抑制肺转移。ATMP 术后给药则无效,而术后给 CY 可明显抑制肺转移。单纯截肢组肺转移瘤结数与对照组相比无显著差异。第 11 天截肢实验组,ATMP 术前连续给药 10 天,结果对原发瘤亦无抑制作用，对肺转移瘤结数的抑制率高达 95%，且有 6/8 的动物完全无肺转移发生。见表 1。

同时证明，ATMP 剂量在 5～20 mg/kg 时，对 LA-795 原发瘤的生长无抑制作用，对肺转移结节数和瘤重抑制率均在 80%以上。见表 2。

组织学检查发现，对照组瘤组织内小静脉、小动脉及淋巴管内可见有瘤栓存在。ATMP 治疗组的瘤细胞形态与对照基本相同，瘤组织血管周围有瘤细胞，但未见侵入血管内(见图 1)。电镜观察，ATMP治疗组瘤细胞核未见明显破坏，与对照组相比，细胞间排列紧密，无明显间隙，间质胶原纤维增多，胞浆内微丝数量较少(见图 2)。

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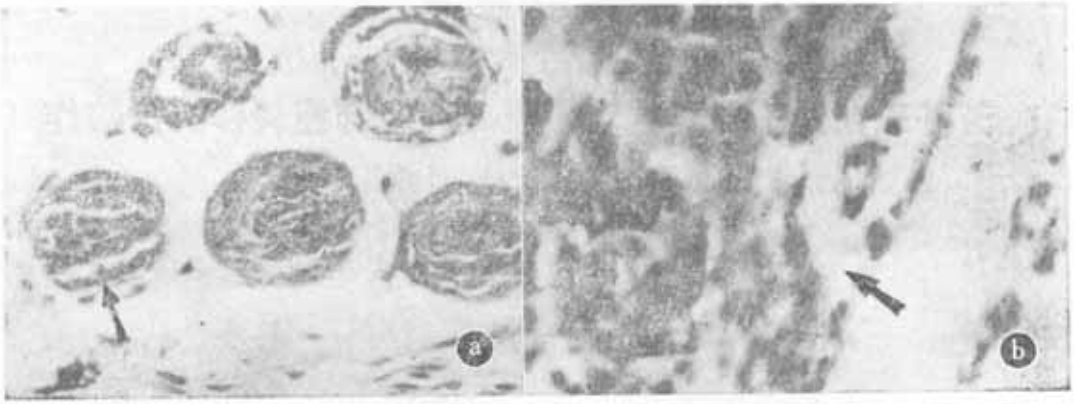

Fig 1. Histological examination on sc Lewis lung carcinoma. A. control group: cancer cells spread into blood vessels ×450 B. ATMP treatment group: no cancer cells were found in the blood vessels ×450

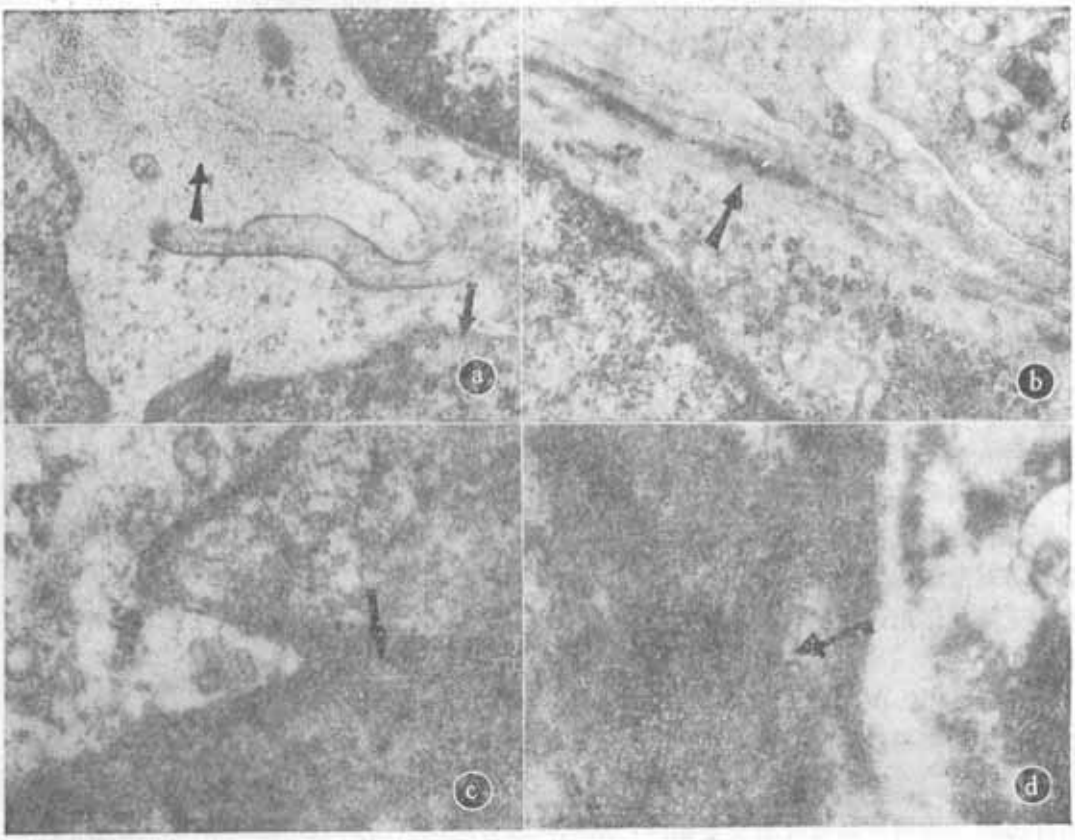

Fig 2. Electron microscopic observation on sc Lewis lung carcinoma. A. control group: the spaces between cancer cells enlarged obviously, gap junctions were absent ×15,000; B. control group: cancer cells have numerous microfilaments ×15,000 C. ATMP treated group: gap junctions and tonofilaments were abundant and there were no spaces between cancer cells; microfilaments were rare ×30,000 D. ATMP treatment group: collagen fibrils were abundant in cells spaces ×30,000.

Tab 1. Effects of ATMP and CY on intramuscularly inoculated Lewis Lung Carcinoma in mice and undergoing surgical removal of primary tumor ($\bar{X}\pm SD$)

Group	Dosage (mg/kg ip)	Treatment schedule (day)	Inhibition rates of im tumor(%)	No. of metastases		Inhibition rates of the number of metastases(%)	Mice free of metastases
				Small	Large		
—	—	—	—	7.7±2.6	0.6±1.0		0/10
Amp$^{\Delta}$	—	—	—	6.5±2.2	1.0±1.1	9.6	0/10
ATMP+Amp$^{\Delta}$	20	1～6	4	1.6±1.5	0	80.7**	3/8
ATMP+Amp$^{\Delta}$	30	6～9	—6.3	3.7±1.3	1.7±1.7	34.9*	0/7
ATMP+Amp$^{\Delta}$	20	10～15	—	8.4±2.9	1.1±1.1	−14	0/8
CY+Amp$^{\Delta}$	18	10～15	—	2.7±1.2	0.1±0.1	66.2**	0/7
—	—	—	—	9.5±5.8	1.1±1.0		0/7
Amp$^{\Delta\Delta}$	—	—	—	7.7±2.0	6.7±2.6	−38.5	0/6
ATMP+Amp$^{\Delta\Delta}$	20	1～10	5	0.3±0.5	0.2±0.4	95.2**	6/8

*$p<0.05$;　**$p<0.01$

$^{\Delta}$ Operation was performed on day 9(1 hr after last drug administration when treatment was given daily on Day 6～9); $^{\Delta\Delta}$ Operation was performed onday 11; Amp=Amputation

Tab 2. Effects of ATMP on sc primary tumor and spontanous metastases of LA-795 Lung adenocarcinoma in mice ($\bar{X}\pm SD$)

Treatment schedule (mg/kg/day) ip	No. of mice initial/end	Inhibition rates of s c tumor (%)	No. of metastases		Weight of metastases (mg)	Inhibition rates of metastases (%)		Mice free of metastases
			Small	Large		No.	Wt.	
—	10/10	—	7.3±3.8	0.3±0.7	2.1±1.9	—	—	0/10
5×14	10/10	5	0.9±0.9	0.1±0.3	0.3±0.3	86.8**	85.7**	2/10
10×14	10/8	26	0.5±0.7	0.	0.05±0.1	93.4**	97.6**	5/8
20×14	10/10	23	0.6±0.7	0.	0.4±0.7	92**	81*	5/10

*　$p<0.05$;　**　$p<0.01$

已有报道[2,3]，肌内接种 Lewis 肺癌一般从第 6 天开始转移。本实验中第 9 天单纯截肢已不能阻止转移的发生。从本文结果可见如在转移发生前采用 ATMP 加截肢的治疗方案可取得明显效果。提示 ATMP 有预防转移的作用。术后无效可能由于此时转移早已开始，并已逐步形成肺转移灶[4]，而 ATMP 在此剂量下不能有效地杀伤瘤细胞。术后给CY仍能抑制转移的发生，可能是由于CY的抗转移作用是直接杀伤细胞所致。组织学观察结果提示，ATMP 抗转移是影响肿瘤转移的早期过程。此与以前的研究结果相符[1]。电镜观察进一步提示，经 ATMP 作用后，Lewis 肺癌组织内超微结构发生了明显变化，而这些变化均与肿瘤细胞的粘连和运动能力的改变有关[5]，因此认为，ATMP 可能抑制了瘤细胞的脱落和运动，因而防止了转移的发生。

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关键词　芳基三氮烯甲氧嘧啶；Lewis 肺癌；LA-795 肺癌；抗转移

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PROPHYLACTICLY ANTIMETASTATIC EFFECTS OF ARYLTRIAZENE METHOXYPYRIMIDINE ON LEWIS LUNG CARCINOMA AND ITS HISTOLOGICAL AND ULTRASTRUCTURAL OBSERVATION

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ABSTRACT The antimetastatic effects of aryltriazene methoxypyrimidine (ATMP) were investigated in mice implanted intramuscularly with Lewis lung carcinoma in the calf of the hind leg. Primary tumor was removed surgically by amputation in mice treated with the tested compounds preoperatively and postoperatively. The results showed that amputation alone on the 9th or 11th day after tumor implantation did not prevent pulmonary metastasis. Prophylactically antimetastatic effects on spontanous metastasis were observed with the treatment of ATMP when neoplasm spreading had not taken place. It was indicated, with histological examination, that after ATMP administration, the cancer cells of primary tumor entering blood and lymphatic vessels were prevented. Observation with electron microscope showed some ultrastructural changes including the strengthening of the gap junction, more abundant of collagen fibrils and lack of microfilament in tumor tissue of ATMP treated group.

The selectively antimetastatic effect of ATMP on LA-795 lung adenocarcinoma was also demonstrated.

Key words Aryltriazene methoxypyrimidine; Lewis lung carcinoma; LA-795 lung adenocarcinoma; Antimetastasis