DOI: 10.3779/j.issn.1009-3419.2012.06.07

·临床研究·

双药方案对比单药方案治疗老年晚期非小细胞肺癌的*Meta*分析

许崇安 昌子又 王小杰 李琳 齐海燕 刘艳

【摘要】**背景与目的** 双药方案治疗老年晚期非小细胞肺癌（non-small cell lung cancer, NSCLC）的疗效是否优于单药化疗尚存争议，本研究旨在对双药方案治疗老年晚期NSCLC患者的有效性和安全性进行系统评价。**方法** 计算机检索PubMed、EMBASE、Cochrane Library、中国期刊全文数据库和中国生物医学文献等数据库，收集双药方案治疗老年晚期NSCLC的随机对照试验，用Stata 11.0软件对数据进行*meta*分析。**结果** 共纳入12项随机对照试验（2,306例病例），*meta*分析结果显示与单药化疗相比双药化疗明显提高了老年晚期NSCLC患者的有效率（OR=1.80, 95%CI: 1.50-2.17, *P*<0.000,1）和1年生存率（OR=1.45, 95%CI:1.22-1.72, *P*<0.000,1）；含铂双药（OR=1.55, 95%CI:1.18-2.03, *P*=0.001）和非铂双药组（OR=1.38, 95%CI: 1.10-1.73, *P*=0.006）的1年生存率均明显高于单药组；含铂双药组更易发生3/4级贫血、中性粒细胞减少、血小板减少和神经毒性（*P*<0.05），非铂双药组毒副反应发生率与单药组相似。**结论** 与单药组相比，双药组可明显提高化疗有效率和生存率，更适合作为老年晚期NSCLC一线化疗方案，但尚需开展针对老年患者的随机对照试验加以验证。

【关键词】肺肿瘤；老年；化疗；*Meta*分析

【中图分类号】R734.2

A *Meta* Analysis of Doublets Versus Single-agent Chemotherapy for Elderly Patients with Advanced Non-small Cell Lung Cancer

Chong'an XU, Ziyou CHANG, Xiaojie WANG, Lin LI, Haiyan QI, Yan LIU

Department of Oncology, the Fourth Affiliated Hospital, China Medical University, Shenyang 110032, China

Corresponding author: Chong'an XU, E-mail: cmu4h-xca@126.com

【**Abstract**】**Background and objective** It remains disputed whether doublets are more effective than single-agent chemotherapy for elderly patients with advanced non-small cell lung cancer (NSCLC). The aim of this study is to evaluate the efficacy and safety of doublets and single-agent chemotherapy for elderly patients with NSCLC. **Methods** Data from all published, randomized trials that compared doublets and single-agent chemotherapy in elderly patients were collected from electronic databases (PubMed, EMBASE, Cochrane Library, CNKI and the CBMdice). *Meta*-analysis was completed using software Stata 11.0. **Results** The results of the *meta*-analysis, including 12 eligible trials (2,306 patients), showed that the doublets significantly increased the overall response rate (OR=1.80, 95%CI:1.50-2.17, *P*<0.000,1) and one-year survival rate (OR=1.45, 95%CI: 1.22-1.72, *P*<0.000,1) compared with single-agent chemotherapy. The results of one-year survival rate in platinum-based doublet chemotherapy arms (OR=1.55, 95%CI: 1.18-2.03, *P*=0.001) and non platinum-based ones (OR=1.38, 95%CI: 1.10-1.73, *P*=0.006) were both significantly higher than that of single-agent chemotherapy. However, grade 3/4 anemia, neutropenia, thrombocytopenia and neurotoxicity (*P*<0.05) were significantly associated with doublet chemotherapy. The incidence of toxicity effect in non platinum-based chemotherapy was similar to that of single-agent chemotherapy. **Conclusion** Compared with single-agent chemotherapy, doublet chemotherapy could increase the overall response rate and one-year survival rate significantly. Therefore, doublet chemotherapy would be more appropriate for elderly patients with advanced NSCLC as the first-line chemotherapy regimen. However, further prospective randomized controlled trials in elderly NSCLC patients is needed to verify the findings in this study.

【**Key words**】Lung neoplasms; Aged; Chemotherapy; *Meta*-analysis

随着人口预期寿命的大幅度提高，其患癌症风险亦随之增加，导致老年人肺癌发病率明显上升[1]。在被确诊的非小细胞肺癌（non-small cell lung cancer, NSCLC）中年龄超过65岁的比例超过50%，其中70岁以上者占30%-40%[2,3]。因此针对这一群体的治疗凸显重要。临床研究[4,5]表明含铂双药方案优于单药或三药联合方案，但

作者单位：110032 沈阳，中国医科大学附属第四医院肿瘤内科（通讯作者：许崇安，E-mail: cmu4h-xca@126.com）

由于纳入和排除标准等限制，老年肺癌在临床试验中的代表人数不足。因此，含铂双药方案仅被证实是适合非老年的晚期NSCLC患者的标准一线化疗方案[6,7]，而老年晚期NSCLC最佳治疗方案仍在争议中。

目前的证据[8-10]表明，与最佳支持治疗相比第三代化疗药物（长春瑞滨、吉西他滨、紫杉醇和多西紫杉醇）单药化疗不但能够延长老年晚期NSCLC患者的生存期，还能提高其生活质量。因此，多数老年晚期NSCLC患者首选第三代化疗药物单药化疗。但也有研究[11-13]表明双药方案联合化疗对老年晚期NSCLC患者同样有效，且毒性可耐受。为明确双药方案与单药方案在治疗老年晚期NSCLC患者中哪一种更具优越性，本研究运用Cochrane系统评价的方法比较两者在有效性和安全性方面的差异，以期为临床决策提供参考依据。

1 材料与方法

1.1 纳入与排除标准

1.1.1 研究设计 随机对照试验（radonmized controlled trails, RCTs），无论是否采用盲法。

1.1.2 研究对象 纳入标准：①病理/经细胞学证实的IIIb期-IV期NSCLC；②既往未接受过其它抗肿瘤治疗并且无化疗禁忌症；③美国东部肿瘤协作组-体力状况（Eastern Cooperative Oncology Group-performance status, ECOG-PS）评分≤2分；④年龄≥65岁。排除标准：①伴有严重内科疾病及感染；②同时伴随其它恶性肿瘤；③肺癌为其它肿瘤转移病灶；④动物实验和体外试验。

1.1.3 干预措施 试验组采用以第三代化疗药物为基础的双药方案化疗，对照组采用单药化疗。

1.1.4 结局指标 1年生存率（化疗后仍然存活1年的患者比例）；化疗有效率（objective response rate, ORR），ORR是指化疗2个周期后按照WHO或RECIST标准达到完全和部分缓解所占的比例；毒副反应，包括血液学毒性和胃肠道反应及神经毒性。

1.2 检索策略 计算机检索PubMed、EMBASE、Cochrane Library、中国期刊全文数据库（CNKI）、中国生物医学文献数据库（CBMdice），检索时间从建库至2011年11月。检索词包括：non-small cell lung cancer、non small cell lung cancer、non small cell lung carcinoma、non small cell lung carcinomas、non small cell lung、NSCLC、malignant epithelial tumor、elderly、pharmacotherapy、antineoplastic combined chemotherapy、非小细胞肺癌、老年、药物治疗、抗肿瘤药物联合化疗等。RCTs检索策略遵循Cochrane系统评价手册5.0，其它检索采用主题词与自由词结合的方式，并根据具体数据库调整，所有检索策略通过多次预检索后确定。同时通过手工搜索相关书籍，挑选相关文章和已发表的文章来补充结果。追查已纳入文献的参考文献，与本领域的专家、通信作者等联系，以获取以上检索未发现的相关信息。当1个会议的摘要与1篇全文都提到了相同的试验时，只评估全文。当2个或更多文章报道相同的数据时，只评估最近、最新的数据。文献语种限中文和英文。

1.3 文献筛选和资料提取 两名研究者交叉核对纳入研究的结果，对有分歧者通过讨论或由第三名研究者仲裁解决。提取的信息资料主要包括：第一作者姓名、发表的杂志和日期、患者的年龄、使用的药物和剂量、患者的数目、1年生存率、ORR以及发生3/4级毒副反应患者的比例。

1.4 文献质量评价 采用Cochrane Handbook 5.0对纳入研究进行方法学质量评价，内容包括：①采用何种随机方法，方法是否正确；②是否进行分配隐藏，方法是否正确；③是否采用盲法，对哪些病例实施了盲法；④有无失访和退出，是否采用意向性（intent-to treat, ITT）分析。依据评价结果，将纳入文献分为A、B、C三个等级。

1.5 统计学分析 采用Stata 11.0软件进行数据分析。双药化疗组作为试验组，单药化疗组作为对照组。在*meta*分析中如果1个试验中有2个以上不同化疗方案的比较，则分别给试验组或对照组的数目记为2次或更多次，因此，实际上比较的组数要多于包含的试验数目。计数资料采用比值比（odds ratio, OR）为疗效分析统计量，各效应量均以95%CI表示。各纳入研究结果间的异质性采用χ^2检验。若$P>0.1$和$I^2<50\%$时，采用固定效应模型进行分析；若存在统计学异质性（$P<0.1$, $I^2>50\%$）时，分析异质性来源，确定是否能采用随机效应模型。如果研究间存在明显的临床异质性，只对其进行描述性分析。必要时采用敏感性分析检验结果的稳定性。

2 结果

2.1 检索结果 按照检索策略和资料收集方法（图1）共查到相关文献1,295篇，通过排除重复、阅读文题、摘要和全文后最终纳入12项RCTs研究[14-25]。所有的数据均从纳入试验中提取。在这些试验中共有2,306例患者，1,055例

患者接受了以第三代化疗为基础的双药方案化疗，1,251例患者接受了单药方案化疗。12项试验中有3项试验最低年龄限制是65岁[18,19,22]，其余9项试验最低年龄限制都是70岁。因为有3项试验有多于2个的对比组[15,16,18]，因此进行对比的组数共有17组。纳入研究的一般特征见表1。

2.2 纳入研究质量评价 9项研究的质量被评为“B”级，3项研究的质量被评为“C”级（表2），尽管所有研究均未提及盲法，且仅1项研究提及分配隐藏，但不会对本研究主要结局指标（1年生存率）产生影响，因此，本研究可信度较高。

2.3 有效率 各研究之间无异质性，采用固定效应模型。12项试验的17个对比组的*meta*分析（图2）表明，与单药化疗相比，双药化疗明显提高了老年晚期NSCLC患者的有效率（OR=1.80, 95%CI: 1.50-2.17, *P*<0.000,1）。

2.4 生存率 各研究间存在明显的异质性（*P*=0.04, I^2=42%），进一步亚组分析显示8项[17,18,20-25]含铂双药方案各研究间无异质性（*P*=0.363, I^2=8.6%），采用固定效应模型合并分析显示，与单药化疗相比含铂双药化疗明显提高了老年晚期NSCLC患者的1年生存率（OR=1.55, 95%CI: 1.18-2.03, *P*=0.001）。4项（8个对比组）[14-16,19]非铂双药方案各研究间存在异质性（*P*=0.003, I^2=55.7%），进一步行敏感性分析，将异质性较大的Gridelli等[15]研究中的吉西他滨联合长春瑞滨对比长春瑞滨单药组剔除后，不但消除了非铂双药方案的异质性，同时也消除了所有试验其余16个对比组之间的异质性。*meta*分析显示非铂双药方案（OR=1.38, 95%CI:1.10-1.73, *P*=0.006）和所有采用双药方案化疗的老年晚期NSCLC患者的1年生存率均明显高于单药化疗者（OR=1.45, 95%CI:1.22-1.72, *P*<0.000,1），见图3。而Gridelli等[15]研究中的吉西他滨联合长春瑞滨组与长春瑞滨单药组的1年生存率相比无统计学差异（OR=0.70, 95%CI: 0.48-1.03, *P*=0.069）。

2.5 毒副反应 由于铂类药物的毒副反应与其它药物明显不同，故将含铂方案和非铂方案的毒副反应分组分析。

2.5.1 含铂双药方案的毒副反应 4项试验[17,21,24,25]报道了3/4级贫血的发生率，4项试验[20,21,23,25]报道了3/4级中性粒细胞减少的发生率，7项试验[17,20-25]报道了3/4级血小板减少的发生率，6项试验[17,20-23,25]报道了3/4级恶心、呕吐的发生率，4项试验[20,21,23,25]报道了3/4级神经毒性的发生率。*meta*分析结果显示含铂双药方案更易发生3/4级贫血、中性粒细胞减少、血小板减少和神经毒性（表3）。

2.5.2 非铂双药组毒副反应 纳入研究[14-16,19]均报道了3/4级贫血、中性粒细胞减少、血小板减少及恶心、呕吐的发生率，3项研究[15,16,19]报道了3/4级神经毒性的发生率。*meta*分析结果显示非铂双药化疗组3/4级毒副反应的发生率与单药化疗组相似（表4）。

2.6 发表偏倚 采用漏斗图对纳入文献潜在的发表偏倚进

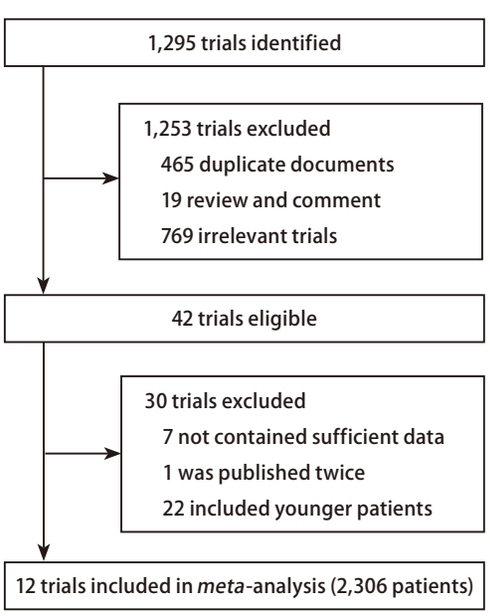

图 1 纳入研究流程图

Fig 1 Trials enrolled in the study

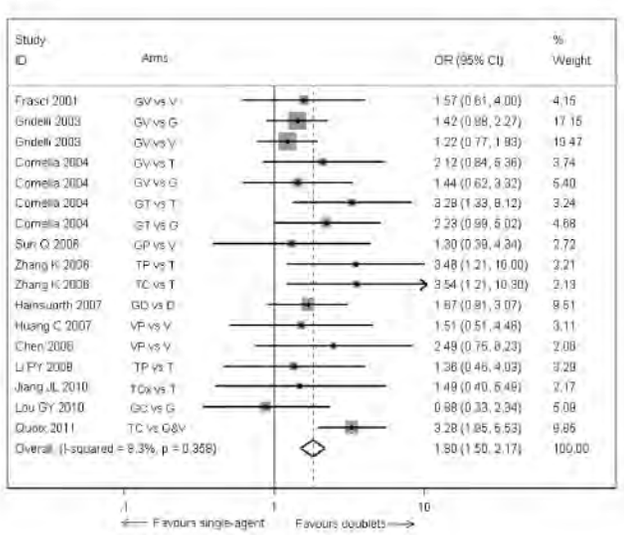

图 2 双药方案与单药方案治疗老年晚期非小细胞肺癌患者的有效率。G：吉西他滨；V：长春瑞滨；T：紫杉醇；D：多西紫杉醇；P：顺铂；C：卡铂；Ox：奥沙利铂。

Fig 2 Comparison of the overall response rate between doublet arms and single-agent arms of the elderly patients with advanced non-small cell lung cancer. G: gemcitabine; V: vinorelbine; T: Taxol (paclitaxel); D: docetaxel; P: cisplatin; C: carboplatin; Ox: Oxaliplatin.

表 1 纳入研究的一般特征

Tab 1 The characteristics of included studies

Reference	Arm	Treatment schedule and dose	No. of patients	Age (yr)	PS	OS (wk)	1-y SR (%)	ORR (%)
Frasci 2001[14] (Lung Cancer)	Traetment	Gemcitabine at 1,200 mg/m² on days 1 and 8, every 3 weeks Vinorelbine at 30 mg/m² on days 1 and 8, every 3 weeks	60	⩾70	16	29	30	22
	Control	Vinorelbine at 30 mg/m² on days 1 and 8, every 3 weeks	60	⩾70	13	18	13	15
Gridelli 2003[15] (J Natl Cancer Inst)	Traetment	Gemcitabine at 1,000 mg/m² on days 1 and 8, every 3 weeks Vinorelbine at 25 mg/m² on days 1 and 8, every 3 weeks	232	⩾70	44	30	30	21
	Control	Gemcitabine at 1,200 mg/m² on days 1 and 8, every 3 weeks	233	⩾70	41	28	28	16
	Traetment	Gemcitabine at 1,000 mg/m² on days 1 and 8, every 3 weeks Vinorelbine at 25 mg/m² on days 1 and 8, every 3 weeks	232	⩾70	44	30	30	21
	Control	Vinorelbine at 30 mg/m² on days 1 and 8, every 3 weeks	233	⩾70	45	36	38	18
Comella 2004[16] (Br J Cancer)	Traetment	Gemcitabine at 1,000→1,200 mg/m² on days 1 and 8, every 3 weeks Vinorelbine at 25→30 mg/m² on days 1 and 8, every 3 weeks	68	⩾70	21	9.7	32	23
	Control	Gemcitabine at 1,200→1,400→1,600 mg/m² on days 1 and 8 and 15, every 4 weeks	68	⩾70	19	5.1	29	18
	Traetment	Gemcitabine at 1,000→1,200 mg/m² on days 1 and 8, every 3 weeks Vinorelbine at 25→30 mg/m² on days 1 and 8, every 3 weeks	68	⩾70	21	9.7	32	23
	Control	Paclitaxei at 100→120→140 mg/m² on days 1, 8 and 15, every 4 weeks	63	⩾70	22	6.4	25	13
	Traetment	Gemcitabine at 1,000→1,200 mg/m² on days 1 and 8, every 3 weeks Paclitaxei at 80→100 mg/m² on days 1 and 8, every 3 weeks	65	⩾70	15	9.2	44	32
	Control	Gemcitabine at 1,200→1,400→1,600 mg/m² on days 1, 8 and 15, every 4 weeks	68	⩾70	19	5.1	29	18
	Traetment	Gemcitabine at 1,000→1,200 mg/m² on days 1 and 8, every 3 weeks Paclitaxei at 80→100 mg/m² on days 1 and 8, every 3 weeks	65	⩾70	15	9.2	44	32
	Control	Paclitaxei at 100→120→140 mg/m² on days 1, 8 and 15 every 4 weeks	63	⩾70	22	5.1	25	13
Sun Q 2006[17] (Chin J Geriatr)	Traetment	Gemcitabine at 1,000 mg/m² on days 1 and 8, every 3 weeks Cisplatin at 20 mg/m² on days 1 to 3, every 3 weeks	22	⩾70	8	9.2	45.5	40.9
	Control	Vinorelbine at 25 mg/m² on days 1 and 8, every 3 weeks	23	⩾70	9	8.8	43.5	34.9
Zhang K 2006[18] (Chin J Clin Oncol)	Traetment	Paclitaxel at 60 mg/m² on days 1, 8 and 15, every 4 weeks Cisplatin at 30 mg/m² on days 2 to 4, every 4 weeks	34	⩾65	-	9	38.2	55.9
	Control	Paclitaxel at 60 mg/m² on days 1, 8 and 15, every 4 weeks	30	⩾65	-	8	36.7	26.7
	Traetment	Paclitaxel at 60 mg/m² on days 1, 8 and 15, every 4 weeks Carboplatin at 5 AUC on days 2, every 4 weeks	32	⩾65	-	10	43.8	56.3
	Control	Paclitaxel at 60 mg/m² on days 1, 8 and 15, every 4 weeks	30	⩾65	-	8	36.7	26.7
Hainsworth 2007[19] (Cancer)	Traetment	Docetaxel at 30 mg/m² on days 1, 8 and 15, every 4 weeks Gemcitabine at 800 mg/m² on days 1 and 8 and 15, every 4 weeks	174	>65	65	5.5	26	25 (126)
	Control	Docetaxel at 36 mg/m² on days 1, 8 and 15, every 4 weeks	171	>65	57	5.1	24	17 (130)
Huang C 2007[20] (J Tianjin Med University)	Traetment	Vinorelbine at 25 mg/m² on days 1 and 5, every 3 weeks Cisplatin at 20 mg/m² on days 2 to 4, every 3 weeks	28	⩾70	-	9.3	46.4	39.3
	Control	Vinorelbine at 25 mg/m² on days 1 and 5, every 3 weeks	30	⩾70	-	9.1	43.3	30
Chen 2008[21] (Lung Cancer)	Traetment	Vinorelbine at 22.5 mg/m² on days 1 and 8, every 3 weeks Cisplatin at 50 mg/m² on days 1, every 3 weeks	34	⩾70	16	11.3	47.2	32.4
	Control	Vinorelbine at 25 mg/m² on days 1 and 8, every 3 weeks	31	⩾70	16	12	50.9	16.1
Li PY 2008[22] (J Clin Pulmonary Med)	Traetment	Paclitaxel at 135 mg/m² on days 1, every 3 weeks Cisplatin at 20 mg/m² on days 2 to 4, every 3 weeks	29	⩾65	-	-	46.4	37.9
	Control	Paclitaxel at 135 mg/m² on days 1, every 3 weeks	29	⩾65	-	-	43.3	31
Jiang JL 2010[23] (Clin J Traditional Med)	Traetment	Paclitaxel at 175 mg/m² on days 1, every 3 weeks Oxaliplatin at 130 mg/m² on days 1, every 3 weeks	18	⩾70	16	11.4	50	44.4
	Control	Paclitaxel at 175 mg/m² on days 1, every 3 weeks	20	⩾70	16	13.2	44	35
Lou GY 2010[24] (Natl Med J China)	Traetment	Gemcitabine at 1,000 mg/m² on days 1 and 8, every 3 weeks Carboplatin at 5 AUC mg/m² on days 2, every 3 weeks	34	⩾70	3	-	32	41
	Control	Gemcitabine at 1,000 mg/m² on days 1 and 8, every 3 weeks	34	⩾70	3	-	31	38
Quoix 2011[25] (Lancet)	Traetment	Paclitaxei at 90 mg/m² on day 1, 8 and 15, every 4 weeks Carboplatin at 6 AUC on day 1, every 4 weeks	225	⩾70	61	10.3	44.5	27.1
	Control	Gemcitabine at 1,150 mg/m² on days 1 and 8, every 3 weeks & Vinorelbine at 25 mg/m² on days 1 and 8, every 3 weeks	226	⩾70	62	6.2	25.4	10.2

→: dose escalation; PS: performance status; OS: overall survival; 1-y SR: 1-year survival rate; ORR: overall response rate.

表 2 纳入研究的方法学质量

Tab 2 Quality assessment of methodology of included studies

Included studies	Randomization	Allocation concealment	Blinding	Lost to follow up	ITT Analysis	Baseline	Quality grading
Frasci 2001[14]	Unclear	Unclear	Unclear	Yes	Yes	Similar	B
Gredelli 2003[15]	Stratified	Unclear	Unclear	Yes	Yes	Similar	B
Comella 2004[16]	Computerized	Unclear	Unclear	Yes	Yesr	Similar	B
Sun Q 2006[17]	Numbered	Unclear	Unclear	Yes	Unclear	Unclear	B
Zhang K 2006[18]	Unclear	Unclear	Unclear	Yes	Yes	Unclear	B
Hainsworth 2007[19]	Unclear	Unclear	Unclear	Yes	Yes	Similar	B
Huang C 2007[20]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	C
Chen 2008[21]	Unclear	Yes	Unclear	Yes	Yes	Similar	B
Li PY 2008[22]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	C
Jiang JL 2010[23]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	C
Lou GY 2010[24]	Numbered	Unclear	Unclear	Yes	Unclear	Similar	B
Quoix 2011[25]	Stratified	Unclear	Unclear	Yes	Yes	Similar	B

ITT: intent to treat.

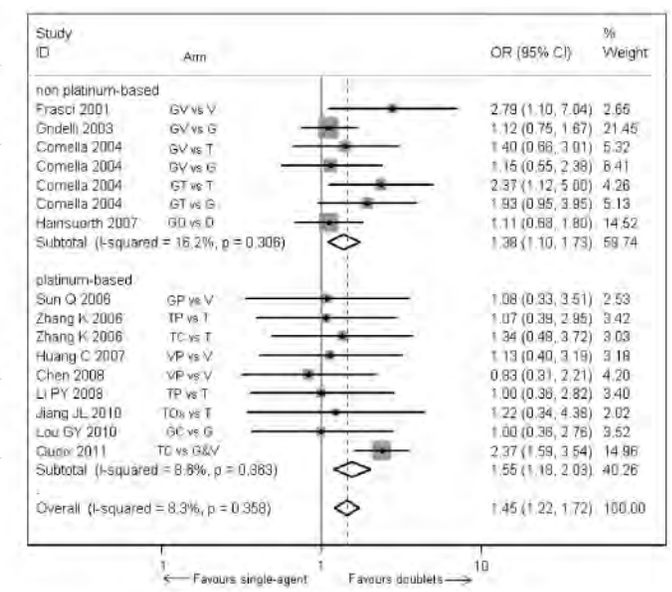

图 3 双药方案与单药方案治疗老年晚期非小细胞肺癌患者的1年生存率。G：吉西他滨；V：长春瑞滨；T：紫杉醇；D：多西紫杉醇；P：顺铂；C：卡铂；Ox：奥沙利铂。

Fig 3 Comparison of the 1-year survival rate between doublet arms and single-agent arms of the elderly patients with advanced non-small cell lung cancer. G: gemcitabine; V: vinorelbine; T: Taxol (paclitaxel); D: docetaxel; P: cisplatin; C: carboplatin; Ox: Oxaliplatin.

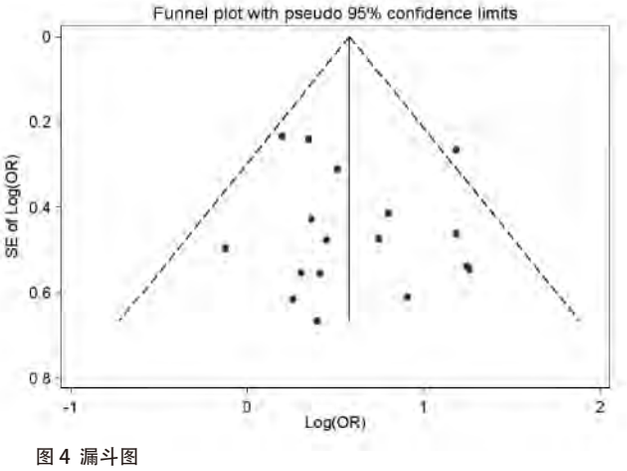

图 4 漏斗图

Fig 4 Funnel plot

表 3 含铂双药与单药化疗的3/4级毒副反应

Tab 3 Comparison of Grade 3/4 toxicity between platinum-based doublet arms and single-agent arms in trials

Toxicity	No. of Trials	No. of patients		OR	95%CI	*P*
		Doublet arms	Single-agent arms			
Anemia	4	487	484	2.21	1.19-4.13	0.013
Neutropenia	4	303	306	5.51	3.67-8.27	<0.001
Thrombocytopenia	7	388	392	5.13	2.48-10.60	<0.001
Nausea & vomiting	6	354	358	7.48	1.00-55.77	0.050
Neurotoxicity	4	303	306	5.5	1.53-19.83	0.009

表 4 非铂双药与单药化疗的3/4级毒副反应

Tab 4 Comparison of grade 3/4 toxicity between non platinum-based doublet arms and single-agent arms in trials

Toxicity	No. of trials	No. of patients		OR	95%CI	*P*
		Doublet arms	Single-agent arms			
Anemia	8	932	926	1.13	0.56-2.30	0.728
Neutropenia	8	932	926	1.28	0.78-2.10	0.324
Thrombocytopenia	8	932	926	1.74	0.88-3.43	0.110
Nausea & vomiting	8	932	926	0.99	0.58-1.70	0.980
Neurotoxicity	7	872	866	1.11	0.44-2.82	0.825

行检验（图4），漏斗图图形基本对称，提示发表偏倚的可能性较小。

3 讨论

随着年龄的增长，化疗危险性亦随之增加[26]，因此，高龄在很多癌症中被当作化疗尤其是联合化疗的绝对或相对禁忌症。但是，由于老年患者是一组异质人群，其生理年龄和实际年龄差异很大，因此单凭年龄并不能决定一个患者是否接受化疗[27]。研究[28-32]表明老年晚期NSCLC患者不但对单药化疗，甚至对双药化疗也有很好的疗效和耐受性。在包括年龄无上限的老年患者的几项大型随机试验[30-34]中，回顾性亚组分析结果显示，采用含铂双药方案化疗的老年晚期NSCLC患者不但肿瘤反应率和总生存与年轻患者相似，而且毒性反应也与年轻患者相似，并没有明显影响老年患者的生活质量。这些数据虽然支持了老年患者使用含铂双药方案化疗的可行性，但是由于他们在试验中的代表人数不足，仅占试验的一小部分，而且是被精心挑选出的能更好耐受化疗的老年群体，并不能代表整个老年人群。因此，双药方案作为老年患者一线优选方案的证据尚不充分，为评价双药方案在治疗老年晚期NSCLC患者中的疗效是否优于单药化疗而进行了本项研究。

研究结果显示，与单药相比双药化疗能够明显提高老年晚期NSCLC患者的有效率。由于各研究间的1年生存率有异质性而进行了亚组分析，结果表明含铂双药各研究间无异质性，合并分析显示与单药化疗相比含铂双药化疗提高了老年晚期NSCLC患者的1年生存率，但也更易发生3/4级血液学和神经毒性。而非铂双药方案各研究间仍存异质性，进一步行敏感性分析发现，剔除异质性较大的Gridelli等[15]研究中的吉西他滨联合长春瑞滨对比长春瑞滨单药组后，不但非铂方案之间异质性消除，而且其余16个对比组间的异质性也随之消除。*meta*分析显示，16个对比组中双药化疗组的1年生存率明显高于单药化疗组；而非铂双药化疗组不但1年生存率明显高于单药化疗组，而且3/4级毒副反应的发生率亦未增加。

尽管本文只纳入了II期/III期RCTs，但在提取数据中，年龄的异质性导致了患者的选择偏倚。在选定的试验中因有2项试验[16,19]的纳入对象中包含了部分体力状态差的年轻患者，导致了研究人群的异质性。但是，由于体力状态差的年轻患者仅占小部分，而且体力状态差亦预示着预后差[27,35]。因此，这种选择偏倚可能对研究结果的影响甚小。虽然不同化疗方案之间可能存在异质性，但有研究[36]表明不同双药方案之间有效率和生存率无统计学差异，因此，不同化疗方案的差异对本研究结果的影响可能较小。

本项研究的质量也受到一些限制，虽然发表偏倚较小，但是由于本项*meta*分析不是基于个体患者资料的数据，而仅仅是从公开发表的文献中提取的数据，因此，治疗效果有可能被过高估计。虽然研究中制定了严格的纳入标准，但各个研究中病例的选择差异、试验设计、药物剂量以及不同药物的联合作用均可产生异质性；并且由于研究结果发表的选择性偏倚，如报道副作用的试验数量少，异质性即使不明显也会显现出来，因此，必须谨慎解释评估的结果。

目前的证据表明，第三代化疗药物单药化疗是非选择的老年晚期NSCLC患者可选择的方案之一，而含铂双药方案作为老年晚期NSCLC患者一线优选方案的证据仍不充分。尽管本项研究显示，含铂双药方案有更高的有效率和生存率，但其毒副反应亦相应增加，因此我们认为可作为体力状态较好患者的选择方案之一；而非铂双药方案不但化疗有效率和1年生存率高于单药化疗组，而且副作用轻微，更适合作为老年晚期NSCLC一线化疗方案。

本次荟萃分析使我们充分认识到，不加选择地将老年晚期NSCLC患者定义为可以或不可以接受单药或双药化疗都是不妥的，应根据老年患者的生理学特性和老年患者的异质性，充分考虑到药物的预期毒性、药代动力学、器官功能和并发症以及患者的意愿进行综合评估化疗的风险/获益比，以使老年晚期NSCLC患者最大获益。今后应进一步开展针对老年晚期NSCLC患者设计的前瞻性随机对比双药与单药的临床试验，为临床决策提供更有说服力的参考依据。

参 考 文 献

1 Lebitasy MP, Hédelin G, Purohit A, *et al*. Progress in the management and outcome of small-cell lung cancer in a French region from 1981 to 1994. Br J Cancer, 2001, 85 (6): 808-815.

2 Ries LAG, Eisner MP, Kosary CL, *et al*. SEER Cancer Statistics Review 1975-2000. http://seer.cancer.gov/csr/1975_2000/, 2005-04-07.

3 Gridelli C, Perrone F, Monfardini S. Lung cancer in the elderly. Eur J Cancer, 1997, 33(14): 2313-2314.

4 Lewis JH, Kilgore ML, Goldman DP, *et al*. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol, 2003, 21(7): 1383-1389.

5 Hutchins LF, Unger JM, Crowley JJ, *et al*. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med, 1999, 341(27): 2061-2067.

6 Pfister DG, Johnson DH, Azzoli CG, *et al*. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol, 2004, 22(2): 330-353.

7 ESMO. ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of non-small-cell lung cancer (NSCLC). Ann Oncol, 2001, 12(8): 1049-1050.

8 Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst, 1999, 91(1): 66-72.

9 Roszkowski K, Pluzanska A, Krzakowski M, *et al*. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer, 2000, 27(3): 145-157.

10 Kudoh S, Takeda K, Nakagawa K, *et al*. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol, 2006, 24(22): 3657-3663.

11 Pujol JL, Milleron B, Molinier O, *et al*. Weekly paclitaxel combined with monthly carboplatin in elderly patients with advanced non-small cell lung cancer: a multicenter phase II study. J Thorac Oncol, 2006, 1(4): 328-334.

12 Maestu I, Gómez-Aldaraví L, Torregrosa MD, *et al*. Gemcitabine and low dose carboplatin in the treatment of elderly patients with advanced non-small cell lung cancer. Lung Cancer, 2003, 42(3): 345-354.

13 Tsukada H, Yokoyama A, Nishiwaki Y. Randomized controlled trial comparing docetaxel (D)-cisplatin (P) combination with D alone in elderly patients (pts) with advanced non-small cell lung cancer (NSCLC): JCOG0207. J Clin Oncol, 2007, 25(18 suppl): abstr 7629.

14 Frasci G, Lorusso V, Panza N, *et al*. Gemcitabine plus vinorelbine yields better survival outcome than vinorebine alone in elderly patints with advanced non-small cell lung cancer. A Southern Italy Cooperative Oncology Group (SICOG) phase III trial. Lung cancer, 2001, 34(Suppl 4): S65-S69.

15 Gridelli C, Perrone F, Gallo C, *et al*. Chemotherapy for elderly patients with advanced non-small cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst, 2003, 95(5): 362-372.

16 Comella P, Frasci G, Carnicelli P, *et al*. Gemcitabine with either paclitaxel or vinorelbine *vs* paclitaxel or gemcitabine alone for elderly or unfit advanced non-small-cell lung cancer patients. Br J Cancer, 2004, 91(3): 489-497.

17 Sun Q, Hua J, Wang Q, *et al*. A randomized control study of treatment of gemcitabine with or without cisplatin for elderly patients with advanced non-small cell lung cancer. Zhonghua Lao Nian Yi Xue Za Zhi, 2006, 25(5): 354-355. [孙清, 华军, 王琦, 等. 吉西他滨加或不加顺铂治疗老年晚期非小细胞肺癌的随机对照研究. 中华老年医学杂志, 2006, 25(5): 354-355.]

18 Zhang K, Hong J, Xie GR, *et al*. Weekly Single-agent versus combination chemotherapy for elderly patients with advanced non-small cell lung cancer. Zhongguo Zhong Liu Lin Chuang, 2006, 33(10): 583-585. [张可, 洪军, 谢广茹, 等. 单药周剂量与联合方案治疗老年晚期非小细胞肺癌的临床观察. 中国肿瘤临床, 2006, 33 (10): 583-585.]

19 Hainsworth JD, Spigel DR, Farley C, *et al*. Weekly docetaxel versus docetaxel/gemcitabine in the treatment of elderly or poor performance status patients with advanced nonsmall cell lung cancer: a randomized phase 3 trial of the Minnie Pearl Cancer Research Network. Cancer, 2007, 110(9): 2027-2034.

20 Huang C, Wang X, Li K. A randomized comparative trial of NVB alone versus NVB plus DDP for treatment of elderly patients with non-small cell lung cancer. Tianjin Yi Ke Da Xue Xue Bao, 2007, 13(4): 543-545. [黄纯, 王璇, 李凯. 诺维本单药及联合顺铂治疗老年晚期非小细胞肺癌随机对照研究. 天津医科大学学报, 13(4): 543-545.]

21 Chen YM, Perng RP, Shih JF, *et al*. A phase II randomized study of vinorelbine alone or with cisplatin against chemo-naïve inoperable non-small cell lung cancer in the elderly. Lung cancer, 2008, 61(2): 214-219.

22 Li PY, Bu BY, Yang JP. Clinical observation of effect of TAX alone versus TAX plus cisplatin for treatment of elderly patients with non-small cell lung cancer. Lin Chuang Fei Ke Za Zhi, 2008, 13(2): 162-163. [李培英, 卜宝英, 杨敬平. 紫杉醇单药及联合顺铂治疗老年晚期非小细胞肺癌的临床观察. 临床肺科杂志, 2008, 13(2): 162-163.]

23 Jiang JL. A comparative trial of paclitaxel plus oxaliplatin-L versus paclitaxel alone for treatment of elderly patients with non-small cell lung cancer. Zhong Yi Yao Lin Chuang Za Zhi, 2010, 22(5): 392-393. [蒋建龙. 紫杉醇联合草酸铂与紫杉醇单药治疗老年晚期非小细胞肺癌的比较研究. 中医药临床杂志, 2010, 22(5): 392-393.]

24 Lou GY, Li T, Gu CP, *et al*. Efficacy study of single-agent gemcitabine versus gemcitabine plus carboplatin in untreated elderly patients with stage IIIb/IV non-small cell lung cancer. Zhonghua Yi Xue Za Zhi, 2010, 90(2): 100-102. [娄广媛, 李铁, 古翠萍, 等. 吉西他滨单药及联合卡铂治疗初治的老年晚期非小细胞肺癌疗效观察. 中华医学杂志, 2010, 90(2): 100-102.]
25 Quoix E, Zalcman G, Oster JP, *et al*. Carboplatin and weekly paclitaxel double chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet, 2011, 378(9796): 1079-1088.
26 Di Maio M, Perrone F, Gallo C, *et al*. Supportive care in patients with advanced nonsmall-cell lung cancer. Br J Cancer, 2003, 89(6): 1013-1021.
27 Azzoli CG, Baker S Jr, Temin S, *et al*. American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small cell lung cancer. J Clin Oncol, 2009, 27(36): 6251-6266.
28 Fidias P, Supko JG, Martins R, *et al*. A phase II study of weekly paclitaxel in elderly patients with advanced non-small cell lung cancer. Clin Cancer Res, 2001, 7(12): 3942-3949.
29 Ricci S, Antonuzzo A, Galli L, *et al*. Gemcitabine monotherapy in elderly patients with advanced non-small cell lung cancer: a multicenter phase II study. Lung Cancer, 2000, 27(2): 75-80.
30 Belani CP, Fossella F. Elderly subgroup analysis of a randomized phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for first-line treatment of advanced non small cell lung carcinoma (TAX 326). Cancer, 2005, 104(12): 2766-2774.
31 Langer CJ, Manola J, Bernardo P, *et al*. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst, 2002, 94(3): 173-181.
32 Lilenbaum RC, Herndon JE 2nd, List MA, *et al*. Single-agent versus combination chemotherapy in advanced non-small cell lung cancer: the cancer and leukemia group B (study 9730). J Clin Oncol, 2005, 23(1): 190-196.
33 Rocha Lima CMS, Herndon JE 2nd, Kosty M, *et al*. Therapy choices among older patients with lung carcinoma. Cancer, 2002, 94(1): 181-187.
34 Hensing TA, Peterman AH, Schell MJ, *et al*. The impact of age on toxicity, response rate, quality of life, and survival in patients with advanced, stage IIIB or IV nonsmall cell lung carcinoma treated with carboplatin and paclitaxel. Cancer, 2003, 98(4): 779-788.
35 Frasci G, Comella P, Panza N, *et al*. Carboplatin-oral etoposide personalized dosing in elderly non-small cell lung cancer patients. Gruppo Oncologico Cooperativo Sud-Italia. Eur J Cancer, 1998, 34(11): 1710-1714.
36 Fisher MD, D'Orazio A. Phase II and III trials: comparison of four chemotherapy regimens in advanced non small-cell lung cancer (ECOG 1594). Clin Lung Cancer, 2000, 2(1): 21-22.

（收稿：2012-01-19 修回：2012-04-09）
（本文编辑 孙丹）

· 启 事 ·

《Thoracic Cancer》被SCI-E收录

2011年6月25日，天津肺癌研究所收到美国Thomson-Reuters公司通知，天津肺癌研究所与Wiley-Blackwell合办的Thoracic Cancer自创刊号起所有文章被SCI-E收录。

Thoracic Cancer（www.thoraciccancer.net）自2010年5月创刊，为全英文季刊，发表肺癌、食管癌、纵隔肿瘤等胸部肿瘤领域的文章，涵盖胸外科学、肿瘤内科学、肿瘤放射治疗学、肿瘤影像医学、分子肿瘤学、肿瘤流行病学等诸多学科。Thoracic Cancer现任主编为天津医科大学总医院周清华教授和中国医学科学院肿瘤医院孙燕院士。

Thoracic Cancer被SCI-E收录，表明了中国胸部肿瘤的临床、科研工作已经得到了国际同行的认可，同时，也为广大的中国胸部肿瘤从业人员提供了向国际同行展示的平台。

SCI-E：Science Citation Index Expanded收录了全球自然科学、工程技术、临床医学等150多个学科领域内8,000多种最具影响力的学术刊物，提供完整的索引、全面的书目记录、详细的作者地址、文章摘要以及每篇文献的参考文献记录、文献的被引用的次数等，是目前国内医学界公认的权威检索系统。