A Meta-analysis of therapy of small cell lung cancer with interferon

Mingyu Shang[1], Zhichun Xiao[2]

[1]Department of Respiratory Medicine, Capital Medical University affiliated Bejjing Anzhen Hospital, Beijing Institute of Heart, Lung and Blood Vessel Diseases
[2]Medical Informatics Center, Peking University, 38 Xueyuan Rd., Haidian District, Beijing
Tel.: +86-10-64456603; Fax: +86-10-64456603; Email: shang_my@163.com

Abstract: Objective: To evaluate the efectiveness and safety of interferon treatment for small cell lung cancer patients. Methods: We electronically searched the chinese academic journals database (1990-2012) and medline (1990-2012). **Results:** The meta-analysis included 5 trials from 86 studies, a total of 587 patients were included in the analysis. The results of meta-analyses showed that the IFN has no effective for 1 and 2 years survival time in small lung cancer patients (95%CI =1.19(0.88, 1.61) and (95%CI =1.44 (0.99, 2.10)). **Conclusion:** IFN has no effective for 1 and 2 years survival time in small lung cancer patients.
[Mingyu Shang, Zhichun Xiao. **A Meta-analysis of therapy of small cell lung cancer with interferon.** *Life Sci J* 2013;10(4):2212-2216]. (ISSN:1097-8135). http://www.lifesciencesite.com. 295

Key words :Interferon;Small cell lung cancer;Meta-analysis

1. Introduction

Lung cancer is one of malignant tumors with high mortality rate in worldwide, patients with small cell lung cancer (SCLC) accounts for about 20% of patients with lung cancer, and it has features of faster clinical progress, shorter survival time, and sensitive to chemotherapy and chest radiotherapy. The total response rate (RR) of limited small cell lung cancer (LD-SCLC) was 80%-90%, the complete remission (CR) was 50%-60%, the median survival time (MST) was 12-20 months, and 2-year disease-free survival rate was 15%-40%; the chemotherapy RR of patients with extensive small cell lung cancer (ED-SCLC) was approximately 60%, the MST was 7-11 months, and 2-year survival rate was less than 5% (Ihde et al.1997). The majority patients present tumor recurrence, and the treatment effect is usually poor with a low MST of 8-12 weeks(Carney et al.,2000). Many scholars consider extending the disease progress with maintenance chemotherapy, however, most experiment results showed that the effect of SCLC maintenance chemotherapy was not good enough, and maintenance chemotherapy would produce side effects to reduce the life quality of patients (Feld et al., 1984). Laurie *et al* (2004) reported that patients with fewer treatment cycles benefited more from second-line treatment after relapse than patients with more treatment cycles. Since 1970s, researchers have found that the immune function of patients with lung cancer was at inhibitory state during diagnosis and therapy process, and the immune status might be associated with survival time. To prolong the survival time of patients with SCLC and maintain life quality, some biological response regulators were added into the standard treatment, such as bacillus calmette-guerin (BCG), interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α) and interferon (IFN). IFN is a group of high activity and versatile inducible protein and glycoprotein produced by stimulated cells, and it induces tumor cell apoptosis and non-apoptotic death through a variety of pathways. The role of IFN has been affirmed in treatment of kidney cancer, malignant melanoma and other solid tumors, but the total survival time of application of IFN to maintenance therapy SCLC after remission remains controversial (Mattson K et al., 1992; Lebeau et al., 1999; Ruotsalainen et al., 2000; Jett et al., 1994; van Zandwijk et al., 1997; Mattson et al.,1997; Kelly et al., 1995). A single study results may be affected by many factors, therefore, Meta-analysis was used to determine the causal relationship between certain intervention factor and disease development (Wang et al., 2002). In this study, we investigated the survival time of patients with SCLC by IFN maintenance therapy via collection of randomized controlled trials which were performed IFN maintenance therapy after SCLC remission.

2.Materials and methods

2.1 Selection of studies

Two authors will take on the review. The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. Two authors will screen the search results and they will read the full text of eligible studies identified in this way. The two authors will decide on their suitability for inclusion in the review based on whether they meet the prespecified inclusion criteria. We will report disagreement and will resolve disagreement by a consensus procedure, if necessary, with a third review author.

2.2 Data extraction and management

Two review authors will extract the data independently to a self-developed data extraction form. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one trial exists, only the publication with the most complete data will be included. We will write to study authors for further information when necessary. Disagreements will be resolved by majority vote, if necessary, of a third review author. One author will enter data into Review Manager software (RevMan 5.0.20), and a second author will independently check the data entry.

2.3 Assessment of risk of bias in included studies

Two authors will independently use the GRADE criteria to assess risk of bias for all included studies.

2.4 Measures of treatment effect

For dichotomous data, results will be summarised as risk ratios(RR), with 95% confidence intervals (CI). For continuous out-comes we will use weighted mean difference (WMD) (when measures are in the same unit), or standardisedmean difference (SMD) (when different scales are used to evaluate the same outcome) with 95% CI as well.

2.5 Unit of analysis issues

Cross-over trials will not be included in this review. We will try to identify cluster-randomised trials; they will be included and analysed in accordance with section 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions.

2.6 Dealing with missing data

The authors of papers withmissing data will be contacted. We will make a note of all trials that do not use intention-to-treat (ITT)analysis; we will make every attempt to analysis our data by this principal.

2.7 Assessment of heterogeneity

I^2 will be used to assess heterogeneity among studies. I^2 > 50% will be considered considerable heterogeneity.

2.8 Assessment of reporting biases

We will assess reporting bias by funnel plots. We will search multiple databases, contact authors, utilize clinical practice guidelines and systematic reviews, to minimize reporting and publicationbias.

2.9 Data synthesis and Sensitivity analysis

A ï¬xed-effects model will be used unless significant heterogeneity with I^2> 50% among studies. In that case a random-effects model will be used.

Subgroup analysis will be used to explore possible sources of heterogeneity. Heterogeneity among studies will be estimated by the I^2 statistic. Typically, values above 50% are deemed to suggest significant heterogeneity. Values of 25% to 50% are deemed to show modest heterogeneity, and values below 25% are deemed to represent low heterogeneity.

We will perform a sensitivity analysis if we find significant heterogeneity (I^2> 50%).

3. Results

3.1 Literature screening

181 articles were searched firstly (including 180 MEDLINE articles and one ASCO meeting abstract), then only five literatures met the inclusion criteria after screening (Mattson K et al., 1992; Lebeau et al., 1999; Ruotsalainen et al ., 2000; Jett et al., 1994; van Zandwijk et al., 1997), and there were a total of 587 cases. The Meta-analysis of 2-year and 1-year survival rate with IFN maintenance therapy after SCLC chemotherapy included 5 literatures (587 cases) and 3 literatures (367 cases), respectively.

3.2 Efficacy analysis

3.2.1. 2-year survival rate of IFN maintenance therapy after chemotherapy remission

The 2-year survival rate of SCLC patients were provided or calculated according to survival curves in the 5 articles. The results showed that there was no advantage about the 2-year survival rate in IFN group than that in control group [RR 1.44, 95%CI (0.99, 2.10)] (Figure 1).

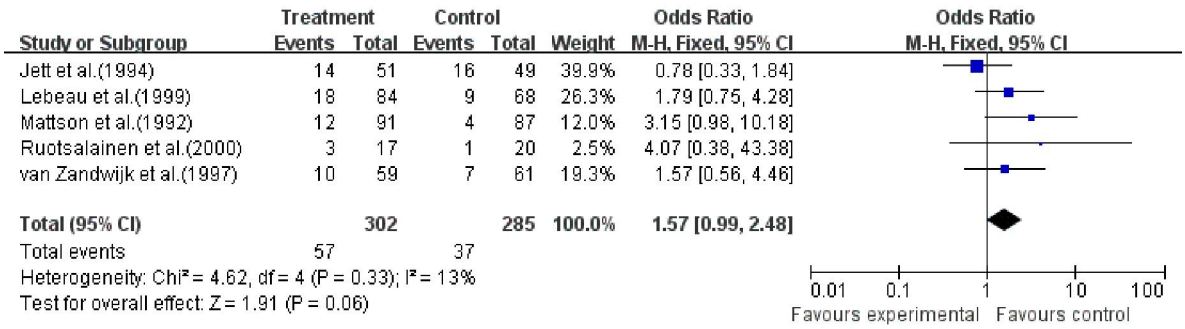

Fig 1. Comparison of 2-year survival rate between IFN maintenance therapy versus control group in the SCLC patients who have responded to chemotherapy.

3.3.2. one-year survival rate of IFN maintenance therapy after chemotherapy remission

The one-year survival rate of SCLC patients were provided or calculated according to survival curves in the 3 articles. The results showed that application of IFN maintenance therapy could not improve the one-year survival rate [RR 1.19, 95%CI (0.88, 1.61)] (Figure 2).

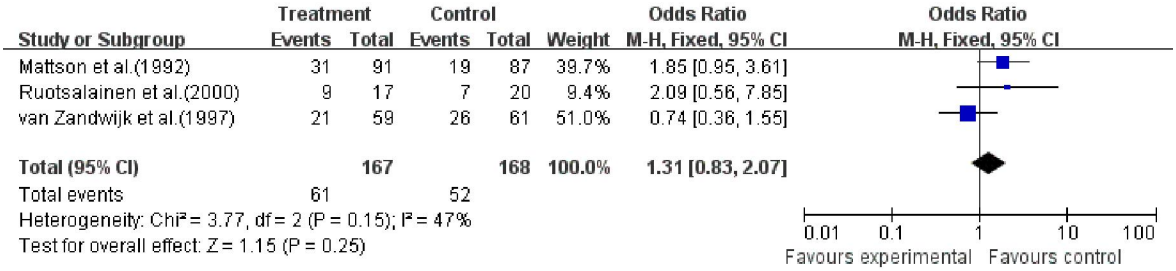

Fig 1. Comparison of 1-year survival rate between IFN maintenance therapy versus control group in the SCLC patients who have responded to chemotherapy.

4. Discussion

The response rate of SCLC chemotherapy is high, but the long-term survival rate is low, which may be related to poor immune function in patients with lung cancer. The immune dysfunction of patients with lung cancer is mainly reflected in the change of T cell function, weaker NK cell killing effect, and macrophage dysfunction, et al (2000). Scholars used IFN and other non-specific immunotherapy to improve immune status and anti-tumor effect, and finally improve the long-term survival of patients. IFN include type Ⅰ IFN (IFN-α and IFN-β) and type Ⅱ IFN (IFN-γ). IFN-α has many biological properties, such as immunoregulatory activity, antiviral activity, cell proliferation interference, regulation of endothelial cell proliferation, endothelial migration, inhibition of angiogenesis, regulation of differentiation and promoting the expression of surface antigens of a variety of cells; it also can present antigens to CTL cells, promote tumor cell non-apoptotic death, and promote cell apoptosis through caspase pathway (Tagliaferri et al., 2005). IFN-β can inhibit tumor cell proliferation and induce tumor cell apoptosis, reduce tumor and viral infections, promote cell expression of MCH-Ⅰ molecule, enhance cell immunogenicity and effector cell sensitivity; it also can inhibit cell cycle of solid tumor cells when IFN-β combined with cytotoxic drugs(Matsumoto et al.,2005). IFN-γ inhibit tumor cells through activation of NK cells and macrophages, and enhance the expression of MHC-Ⅱ antigens, however, the anti-tumor effect of itself is very weak(Zika et al.,2005). In recent years, it has been found that IFN was able to affect the cell contact and signal transduction(Tagliaferri et al.,2005). With the development of gene recombinant technology, the purified IFN has been widely used in clinic, and it has been confirmed that IFN played an important role in malignant melanoma, renal cell carcinoma, AIDS-related Kaposi sarcoma, follicular lymphoma, leukocyte leukemia, chronic myeloid leukemia and other malignancies. In recent 30 years, it has been proved that IFN-α and IFN-β could inhibit the growth of lung cancer cells *in vitro* and animal models, and increase the chemotherapy and radiotherapy effects of lung cancer cell line (Ruotsalainen et al., 2002). At first, *Jones* used IFN-β to treat 10 cases of SCLC, but no tumor shrinkage in all patients, for this negative results, *Jones* proposed IFN should not be used alone when there were higher tumor burden, and to maintain stable disease status, a large dose of IFN were not required; however, it should extend the low dose treatment time. He also proposed that IFN could be used as maintenance therapy or in combination with chemotherapy (Jones et al.,1983). Phase Ⅰ and Ⅱ clinical studies found that combination of IFN and chemotherapy could improve SCLC chemotherapy remission rate, and IFN maintenance therapy could prolong survival after remission, however, the results of phase Ⅲ randomized controlled study were not consistent.

During the evaluation of clinical interventions, large sample RCT with good design and implementation and its evaluation system is the gold standard (Villar et al.,1995). Meta-analysis is essentially an observational study, it is a summary analysis of previous published papers, however, due to various limitations, and it is likely to produce bias in each step. The bias of Meta-analysis can be divided into three categories: sampling bias, selection bias and research bias. In this study, we didn't limit the range, years and sample size when we made retrieval strategy. When reading the title and abstract, we excluded phase Ⅰ and Ⅱ clinical trials without control group, non-randomized, retrospective controlled study, then we read the full text, and there were two repeat published studies and we excluded

one. In order to reduce sampling bias, we also searched conference abstracts, other data bases and references. However, "reduce" is not equal to "eliminate", the "funnel plot" analysis showed asymmetry, mainly due to the presence of publication bias, which suggested the negative results might not be published. In addition, the small sample size is also related to asymmetry funnel plot. In this study, one literature was removed because most enrolled patients failed to complete treatment; one high-quality research was also not included because the survival data was not obtained from the author, which has some influence on this study. *Mattson* divided patients into three groups after chemotherapy remission: maintenance chemotherapy, IFN maintenance treatment and observation, during the treatment process, the author found that maintenance chemotherapy didn't have survival advantage, and damaged the life quality of patients, so the chemotherapy group was terminated in advance; which resulted in uneven patients in each group and the baseline inconsistencies, however, it didn't affect the randomness between IFN group and control group, so it was included in this study.

We should pay attention to patients' "values and willingness" in evidence-based practice, which would help to improve patients' compliance. *Kelly* used IFN-α-2a to maintenance therapy SCLC patients for two years, which failed to extend the remission and survival time. Many patients withdrew from the study because of the low degree of toxicity (≤3 level). Due to the long-term medication, patients didn't want to withstand long time treatment, even the toxicity was minimal, and only one patient took drugs for two years. The negative results were caused by poor tolerance and unfinished treatment. Therefore, in the future, we must consider the patients' "values and willingness" to maintain case number.

In our study, the included five literatures are all prospective studies, which described the lost and withdraw. In which, 2 literatures didn't provide random grouping method, 2 literatures provided raw data and other 3 articles estimated the survival rate and number from the survival curves. In this study, we did not only make the Meta-analysis of one-year and two-year survival rate of SCLC patients with IFN, but also the subgroup analysis of IFN-α. The Meta-analysis of 2-year survival rate suggested IFN maintenance therapy had no advantage compared to control group [RR 1.44, 95%CI (0.99, 2.10)] (Figure 1). The Meta-analysis of one-year survival rate also showed that IFN maintenance therapy could not improve one year survival rate [RR 1.19, 95%CI (0.88, 1.61)] from 3 literatures (Figure 2). In the sensitivity analysis, it is considered that IFN-γ has weak anti-tumor effect, so we excluded 2 studies which was about IFN-γ maintenance therapy; the subgroup analysis of IFN-α maintenance therapy showed the 2-year survival rate was [RR 2.08, 95%CI (1.16, 3.72)] and one-year survival rate was [RR 2.99, 95%CI (1.13, 7.93)], which suggested IFN-α maintenance therapy could significantly improve the one-year and 2-year survival rate (Figures 3 and 4). Because malignancy is a multifactorial disease, which has lots of prognostic factors and confounding factors; IFN therapy needs long follow-up and may cause higher lost, the side effects also will reduce the patients' compliance and affect the research results. Therefore, in the sensitivity analysis of our study, IFN-α was used alone to perform Meta-analysis, which showed that IFN-α might play a more important role in improvement of one-year and 2-year survival rate with IFN.

Our results showed that IFN maintenance therapy didn't improve the one-year and two-year survival rate of SCLC patients after chemotherapy remission, but IFN-α improved the survival rate. However, due to the fewer included cases and bias, we didn't analyze LD-SCLC and ED-SCLC. Our results also suggested that IFN-α significantly increased the survival rate, not IFN-γ, it still needs to further confirm with multi-center, large sample, randomized controlled studies.

Correspond to:
Mingyu Shang
2# Anzhen Road, Chaoyang district, Beijing 100048, China.
Tel.:+86-10-64456603;
Fax:+86-10-64456603;
Email: shang_my@163.com

References

1. Ihde DC, Pass HI, Glastein E. Small cell lung cancer. In: De Vita VT Jr, Hellman S, Rosenberg SA(eds). Cancer Principles and Practice of Oncology, 5th ed. Philadelphia: Lippincott-Raven; 1997. 911 – 949. Chemotherapy, in Hansen HH: Textbook of Lung cancer. London, Martin Donitz LTD; 2000. 261 – 272.
3. Feld R, Evans WK, DeBoer G, et al. Combined modality induction therapy without maintenance chemotherapy for small cell carcinoma of the lung. J Clin Oncol, 1984; 2(4): 294 – 304.
4 .Laurie SA, Logan D, Markman BR, et al. Practice guideline for the role of combination chemotherapy in the initial management of

limited-stage small-cell lung cancer. Lung Cancer, 2004; 43: 223 – 240.
5 Mattson K, Niiranen A, Pyrhonen S, et al . Natural interferon alfa as maintenance therapy for small cell lung cancer. Eur J Cancer, 1992; 28: 1387 – 1391.
6 Lebeau B, Delasalamoniere P, Ozeanne G, et al. alpha Interferon as maintenance therapy for small cell lung cancer(SCLC). J Clin Oncol, 1999; 17(suppl): 1832.
7 Ruotsalainen T, Halme M, Isokangas OP, et al.Interferon-alpha and 13-cis-retinoic acid as maintenance therapy after high-dose combination chemotherapy with growth factor support for small cell lung cancer--a feasibility study. Anticancer Drugs, 2000; 11: 101-108.
8 Jett JR, Maksymiuk AW, Su JQ, et al . Phase III trial of recombinant interferon gamma in complete responders with small-cell lung cancer. J Clin Oncol , 1994; 12: 2321-2326.
9 van Zandwijk N, Groen HJ, Postmus PE. Role of recombinant interferon-gamma maintenance in responding patients with small cell lung cancer. A randomised phase III study of the EORTC Lung Cancer Cooperative Group. Eur J Cancer, 1997; 33: 1759-1766.
10 Mattson K, Niiranen A, Ruotsalainen T. Interferon maintenance therapy for small cell lung cancer: improvement in long-term survival. J Interferon Cytokine Res , 1997; 17: 103-105.
11 Kelly K, Crowley JJ, Bunn PA Jr. Role of recombinant interferon alfa-2a maintenance in patients with limited-stage small-cell lung cancer responding to concurrent chemoradiation: a Southwest Oncology Group study. J Clin Oncol, 1995; 13: 2924-2930.
12 Wang JY. Chief Editor. Evidence-Based Medicine and Clinical Practice. 1st edition. Beijing: Science Press; 2002. 55 – 81, 86 – 121.
13 Zhu XS, Shao L. Immune status of lung cancer patients and immunotherapy of lung cancer. Chinese J. Lung Cancer 2000; 3: 158-160.
14 Tagliaferri P, Caraglia M, Budillon A. New pharmacokinetic and pharmacodynamic tools for interferon-alpha (IFN-alpha) treatment of human cancer. Cancer Immunol Immunother, 2005; 54: 1 – 10.
15 Matsumoto K, Okano J, Murawaki Y. Differential effects of interferon alpha-2b and beta on the signaling pathways in human liver cancer cells. J Gastroenterol, 2005; 40: 722 – 732.
16 Zika E, Fauquier L, Vandel L. Interplay among coactivator-associated arginine methyltransferase 1, CBP, and CIITA in IFN-gamma-inducible MHC-II gene expression. Proc Natl Acad Sci USA , 2005; 102: 16321-16326.
17 Ruotsalainen TM, Mattson K. Interferon trials in small cell lung cancer at one institution: a comparison of results obtained before and after initiation of systematic treatment trials using IFN-alpha in combination with other modalities. J Interferon Cytokine Res, 2002; 22: 165-171.
18 Jones DH, Bleehen NM, Slater AJ. Human lymphoblastoid interferon in the treatment of small cell lung cancer. Br J Cancer, 1983; 47: 361-366.
19 Villar J, Carroli G, Belizan JM. Predictive ability of meta-analyses of randomised controlled trials. Lancet, 1995, 345: 772 – 776.
20 Zhang MM, Li J. Evidence-based medicine: from a point of view of patient. Medicine and Philosophy, 2005; 26: 55 – 56.

11/10/2013