Meta-analyses of clinical trials in patients with non-small cell lung cancer
Minireview

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Currently lung cancer is the most common worldwide cause of major cancer incidence and mortality. The treatment outcome is poor and there are still many questions which remain unanswered such as the interest of the best treatment schedule. To approach the answer what is the best treatment for patients with non-small cell lung cancer (NSCLC) we made a review of the published meta-analyses. Meta-analysis is a systematic approach to identification and abstraction of critical information from different randomized, controlled trials. The review of meta-analyses of clinical trials we had made showed that

– in radically operated patients the postoperative radiotherapy should be detrimental if standard fields are used;

– postoperative chemotherapy with regimens based on cisplatin has an absolute benefit of 5% at 5 years survival;

– we can improve the survival of patients with locally advanced NSCLC using chemoradiation comparing to radiotherapy alone;

– chemotherapy with cisplatin can prolong the survival and improve the quality of life in patients with advanced NSCLC;

– platinum-based doublets remain the standard regimen in patients with advanced NSCLC;

– there is a slight but significant improvement in efficacy of gemcitabine plus platinum agent when compared with other platinum based comparators in regard to the survival and time to disease progression.

In our dealing with NSCLC patients there are still many controversial opinions, and the meta-analyses are seldom the only way to find more effective treatment regimen, while the improvement in lung cancer treatment is a story of small steps.

Key words: meta-analysis, non-small-cell lung cancer, chemotherapy, radiotherapy, surgery

Currently lung cancer is the most common worldwide cause of major cancer incidence and mortality [34]. It is estimated that lung cancer has accounted for over 169,500 new cases in the United States during 2001 and over 157,400 cancer deaths [19]. It is the most frequent cancer as well, and it causes the most common cancer related death in Slovenia [9].

Efforts, how to avoid the disease with preventive measures, have a limited effect [52]. In the same manner the secondary prevention – to find patients in the early phase of disease - takes a normal course only studiedly and there is no randomized trial demonstrating reduction in lung cancer mortality by screening [6, 30, 46]. It is not an unusual opinion that, despite major advances in the understanding of the biology of lung cancer, no significant improvement in the survival has occurred in the past two decades [51]. In Slovenia the relative 5-year survival rate was only 3% higher in years 1993–97 than in 1983–87. The survival increased just in patients with localized diseases, what may be attributed to the improved accuracy of disease staging [35]. Can meta-analysis show more optimistic assessment?

What is meta-analysis?

Meta-analysis is a systematic approach to identification and abstraction of critical information from different randomized, controlled trials. But we do not forget that the value of information of meta-analysis is nevertheless limited. Namely, there exist discrepancies between meta-analyses and subsequent large randomized, controlled trials [26]. However, the value of meta-analysis increases if it is made on individual patient data and not on basis of the

literature [50]. Doing a meta-analysis correctly demands expertise in both the method and the substance and hence almost always requires a collaboration between clinicians and experienced statistician. Just only meta-analysis often enables statistical significant results from some small randomized controlled trials, where the results can be non significant or controversial [4].

Can be meta-analyses replaced with preclinical studies?

It is hopeless to replace meta-analyses of clinical studies with preclinical studies. All clinical studies must be preceded with *in vitro* experiments which just show, whether drugs are effective and whether clinical studies are reasonable or not.

But good preclinical results do not necessarily lead to a good clinical outcome. Such as *in vitro* drug sensitivity testing of cell lines derived from the patient tumor can correlate with the clinical response but does not significantly correlate with the patient survival [42]. Therefore, large clinical trials or meta-analyses of smaller trials will be furthermore necessary to improve the survival of lung cancer patients.

Meta-analysis and postoperative radiotherapy in patients with non-small cell lung cancer (NSCLC)

One of the methods how to improve the survival of the NSCLC patients is a multimodality treatment. Thus, there were many attempts with postoperative radiotherapy (PORT) [8, 11], but it remains controversial regardless of meta-analysis, which has almost solved some dilemmas. Namely, it showed that the survival of NSCLC patients with stages I and II was reduced using PORT [8]. Meta-analysis also showed a disadvantage with the use of PORT regarding the local recurrence-free survival. There was no difference in the results between different groupings concerning the total planned dose (<60 Gy or 60 Gy) and there was no suggestion that the treatment effect differed between trials using different types of radiotherapy.

However, there are opposite findings in the recent randomized trial which included patients with pathological stage I [53]. PORT was a clearly protective factor when the local control was considered (2.2% *versus* 23% local recurrences) and the overall 5-year survival and disease-free survival showed a favorable positive trend (67% *vs.* 58%, p=0.048 and 71% *vs.* 60%, p=0.039, respectively). Moreover, functional results demonstrated that there was no clinical significant deterioration in the postoperative lung function. It seems that the main reason for such results was the average treatment field, which did not exceed 50 cm^2, while the average treated area surface ranges from 72 to 150 cm^2 [56]. The rationale for such a small treatment area is based on the fact that all patients underwent a radical hilar and mediastinal lymphadenectomy and pathology confirmed a pN0 status.

In this trial much less patients were included than in meta-analysis (104 *vs.* 516 patients with stage Ia and Ib) and the authors were invited to join the PORT meta-analysis group and contribute their data when the individual patient data meta-analysis is updated [49]. Until these new results have not been brought out conclusion still remains that PORT should be detrimental to patients with completely resected early stage NSCLC and should not be used routinely but that new randomized clinical trials should be desired.

In spite of the observation of meta-analysis that PORT was detrimental in stage I and II of NSCLC, there is a completely different conclusion in patients with stage IIIa of NSCLC [8]. Actually, in patients with locally advanced disease the 5-year overall survival showed a promising trend, PORT was beneficial, but it was not statistically significant and new clinical trials are really necessary.

Meta-analysis and postoperative chemotherapy in patients with NSCLC

In a relevant meta-analysis updated data on individual patients from 52 randomized clinical trials were used. It was found out that there was a small survival advantage using cisplatin based chemotherapy in all stages of NSCLC. This recent overview analysis was based on patients' data from all traceable (till 1995) randomized trials [33].

The same meta-analysis offers hope of progress and suggests that chemotherapy may have a role in postoperative treating NSCLC [33]. It was shown from 14 randomized clinical trials (4357 patients) that postoperative chemotherapy with regimens based on cisplatin had an absolute benefit of 5% at 5 year survival but results were not conclusive.

On the other hand, a recent multicentric study shows statistical significant benefit of adjuvant cisplatin based chemotherapy which was given after the complete resection of NSCLC [1, 25]. In the pStage I, II and IIIa the 5-year overall survival was 5% better compared to the group of patients with postoperative chemotherapy and the group where only surgery was performed (45% *vs.* 40%). Also the disease-free survival was 5% better (39% *vs.* 34%) in the group receiving postoperative chemotherapy.

There are some other ongoing phase III trials comparing surgery alone and surgery followed by adjuvant chemotherapy (NCI-Canada trial, ANITA1, ANITA2 and the Big Lung Trial led by the Medical Research Council) as well as the planned LACE meta-analysis of the new generation of trials, which will include over 4,000 patients and will be of major importance [22].

Meta-analysis and preoperative chemotherapy in patients with NSCLC

Recent experience has emphasized the need to include systemic chemotherapy in the combined-modality management of locally advanced non-small cell lung cancer stage III. If definitive surgery is planned, the preoperative application of chemotherapy may have many advantages in comparison to the postoperative delivery. Patients compliance to receive full doses of chemotherapy, possible locoregional downstaging, and frequent postoperative problems following complete resections are some of the arguments favoring the preoperative chemotherapy [7]. Despite numerous phase-II investigations, little evidence from the randomized phase-III trials has been generated [39, 48, 54, 57]. Early inclusion of radiotherapy prior to the definitive resection may help to improve the preoperative downstaging. Besides the available mature phase-II data, phase-III results from the randomized trials lack to define the overall value of such a complex approach.

There are only three completed and already published phase III studies comparing preoperative chemotherapy and surgery to simple surgery [13, 37, 38]. Although the long-term overall survival difference did not reach statistical significance in the largest study [13], all 3 trials are in favor of preoperative chemotherapy. As the benefit of preoperative chemotherapy seems to be greater in early stage, a systematic meta-analysis using individual data of all completed and ongoing trials should be made. Because of the lack of statistical power for definitive conclusions, the preoperative chemotherapy should not be a standard of care for the operable NSCLC but only a part of randomized trials.

Important issues in the future will also aim at individualizing these intensive programs according to the findings in clinical prognostic factor analyses and to prospectively validate the prognostic risk stratification. Data from the translational and molecular research may further help to develop such evidence-based guidelines [15].

Locally advanced NSCLC

Meta-analysis of trials comparing radiotherapy *versus* radiotherapy plus chemotherapy

In spite of the fact that the treatment management of stage III of NSCLC remains highly controversial, and the roles of surgery, chemotherapy, and radiotherapy are hotly debated, the main advances were obtained from the combined strategies. There are data which show better survivals in the group of patients treated with chemoradiation comparing to radiotherapy alone [14, 40].

Meta-analysis of the twelve randomized trials in patients with unresectable NSCLC (stage IIIa and IIIb), which was not made with individual patient data, has shown the results favorable to radiotherapy combined with chemotherapy comparing to radiotherapy alone [29]. In another meta-analysis using updated data on individual patients from 52 randomized clinical trials improved survival in patients with chemoradiation was observed [33].

We have not found the same results with the low dose chemotherapy, which is administered simultaneously during the course of radiotherapy to achieve a radiation sensitizing effect. During the last decade there have been at least four randomized trials, which evaluated either cisplatin or carboplatin as a single agent given in low doses concurrently with thoracic radiation, but only in one of the studies the sensitizing with cisplatin significantly prolonged the survival [41]. A meta-analysis was not made.

In many centres combined modality treatment has replaced radiation alone as the primary treatment for the locally advanced NSCLC. Full doses of older platinum containing regimes have been given either concurrently or sequentially in two phase III trials and in each study improved survival was observed in patients treated with simultaneous chemoradiation [10, 16]. The latest meta-analysis, based on the literature, showed no significant difference in mortality or toxicity between the weekly and daily regimens [36]. Currently it appears that giving full dose, older chemotherapy regimens simultaneously performed with thoracic radiation represent the most effective treatment for good performance stage III NSCLC patients. But more results are necessary to confirm this opinion [2, 31].

There are also several attempts to treat patients with newer drugs and platinum. Most of these new regimens (gemcitabine-cisplatin, paclitaxel-cisplatin, and vinorelbine-cisplatin) could not be used simultaneously at full dose with thoracic radiation [55]. The optimum way of integrating thoracic radiation with newer cytotoxic and biologic targeted agents remains to be determined.

Advanced NSCLC

Meta-analysis of trials comparing supportive care *versus* supportive care plus chemotherapy

There were many studies which showed that chemotherapy with cisplatin can prolong the survival and improve the quality of life in patients with advanced NSCLC. Therefore, the result of the above mentioned meta-analysis of updated data on individual patients was not surprising, but it was much more conclusive [33]. Data were available from 11 trials (1190 patients). Two trials used long term alkylating agents and one used etoposide as a single agent. The remaining 8 trials (778 patients) used cisplatin based che-

motherapy and these regimens were much more effective than those with alkylating agents or etoposide alone ($p<0.0001$).

The cisplatin based trials showed a benefit of chemotherapy ($p<0.0001$) with a reduction in the risk of death of 27%, equivalent to an absolute improvement in the survival of 10% (5% to 15%) at one year, or an increased median survival of 1.5 months (1 months to 2.5 months) comparing with the best supportive care.

There are also two another meta-analyses, which compared polychemotherapy and the best supportive care in patients with advanced NSCLC. However, they were not using only updated data on individual patients but mostly data from the literature. The first one showed a reduction in mortality during the first 6 months with polychemotherapy and an improved quality of life. They conducted a meta-analysis of published and unpublished seven randomized clinical trials with more than 700 patients with non-resectable NSCLC [47]. The second one showed an increase in median survival from 3.9 months for the best supportive care to 6.7 for chemotherapy [28].

Although modest, such improvements can (given the high incidence of lung cancer) be important in public health terms. The studies of patients' opinions of treatments accept considerable toxicity in return for small improvements in the survival [45].

Advanced NSCLC
Do platinum-based doublets remain the standard regimen?

Chemotherapy prolongs the survival and palliates symptoms compared with the best supportive care in patients with the advanced NSCLC. Although the addition of a drug often increases the response rate, the impact on the survival is still controversial. The literature-based meta-analysis of 33 trials showed a significant increase in the response rate, 1-year survival and median survival in favor of two drugs comparing one ($p<0.001$) which was actually not controversial. But it could not show the same benefit in 3-drugs regimen comparing 2-drugs regimen [12]. In this part of meta-analysis of 32 trials there was only a significant increase in the response rate ($p<0.001$) in favor of 3-drugs and very modest increase in 1-year survival ($p=0.30$) and median survival ($p=0.12$).

Another of the recent literature-based meta-analysis yielded comparable results [3]. The meta-analytic procedure of 17 trials also showed a significant increase in the response rate (17%) and 1-year survival (4%) in favor of two drugs comparing one. However, in 11 trials there was not significant slight benefit in response rate of 3-drugs regimen (2%) and furthermore an absolute average decrease in 1-year survival of 4%.

So, doublet regimens remain the standard chemotherapy in advanced NSCLC. The data support that deleting one drug compromises the response and survival, except in the elderly patients who are not suitable for platinum-based therapy [21]. On the other hand, adding one drug may increase the response but has no effect on the survival. These results of the literature-based meta-analysis should be confirmed by meta-analysis based on the individual patients data.

Advanced NSCLC
Is there the best chemotherapy regimen?

The introduction of several new antineoplastic agents including the taxanes, gemcitabin, vinorelbine, and irinotecan has resulted in improved treatment for patients with advanced NSCLC. Several of these agents, when combined with either cisplatin or carboplatin, have resulted in improved median and 1-year survival when compared to randomized trials with either cisplatin alone or older cisplatin-based combination regimens [5, 23, 24]. However, there are still insufficient data, whether any new drug is more effective than the other new agents.

There is a very known randomized ECOG study which compared four combinations of the new antineoplastic agents in the treatment with cisplatin/paclitaxel, cisplatin/gemcitabin, cisplatin/docetaxel, and carboplatin/paclitaxel [44]. The response rate, median survival, 1-year and 2-year survival did not differ significantly in patients receiving any of the four regimens, but it was seen that the treatment with cisplatin/gemcitabin was associated with significantly longer time to the progression of disease. In spite of another big randomized study, which also did not show any advantage between cisplatin/gemcitabin, carboplatin/paclitaxel and cisplatin/vinorelbin [43], the above mentioned reduction in time to the progression in ECOG study [44] was used as a background of the new meta-analysis [24].

This new meta-analysis was presented at the 10th World Conference on Lung Cancer and the data were published only in the abstract form [24]. They analyzed 13 randomized trials and found a significant reduction in mortality in favor of the patients treated with cisplatin/gemcitabin regimen. An absolute overall survival improvement was 3.9% at 1 year and the improvement of progression-free survival was 4.2%. There was a slight but significant improvement of one new regimen compared with platinum based comparators. With all high opinion, we have to say that this improvement of efficacy was reached by comparing cisplatin/gemcitabin regimen with so many different drugs regimens that the results might not be conclusive. We are still waiting for the data to be published in order to be able to make comparison only among new drug regimens.

There is no meta-analysis to show that the combination of the two new cytostatic drugs is more effective than the com-

bination of the new drug and cisplatinum. But, up to the present the published trials showed that the both drug combinations had comparable activity in patients with advanced cancer [17]. There was no difference in median duration of response, time to tumor progression, overall survival, or 1-year or 2-year survival rates. However, the combination gemcitabin/docetaxel had the more favorable toxicity profile (particularly less neutropenia) than the combination docetaxel/cisplatin.

Similarly, no statistically significant difference was seen in the survival berween the two new antineoplastic agents (paclitaxel/gemcitabin) and carboplatin *versus* the paclitaxel/carboplatin chemotherapy [20], though the combination paclitaxel/gemcitabin/carboplatin gave a better response rate, median progression-free survival and median overall survival.

In conclusion, as meta-analyses show a small survival advantage using specific treatment, it is evident that there will be still a gap between the best treatment and that which is actually delivered [18, 27]. However, it is not clear which regimen to prefer, since cost and toxicity are great concern, especially if benefits are small. In this way it is understandable that the clinical research in the field of lung cancer has not contributed enough to shape the best standard treatment [32].

On the other hand, the improvement in lung cancer treatment is a story of small steps and the meta-analyses are occasionally the only way to find more effective treatment regimen.

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