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Pre-operative chemotherapy: Another treatment option for resectable non-small cell lung cancer

Introduction

Lung cancer is a major health problem globally, with 1.5 million cases diagnosed each year. Most of these cancers (85%) are non-small cell lung cancers (NSCLC). Lung cancer has a high mortality rate, with only around 8% survival at 5 years. For early-stage disease (Stage I or II) surgery is regarded as the best treatment approach. However, adding chemotherapy either before or after surgery may help improve survival and reduce disease recurrence.

There is good evidence that post-operative chemotherapy, with or without radiotherapy, improves survival. Most guidelines on the treatment of NSCLC now recommend this treatment. There could also be advantages in giving chemotherapy before surgery. It might reduce the size of the tumour, increase operability, eradicate micro-metastases, and be better tolerated before than if chemotherapy is given after surgery. However, there has been uncertainty about the effectiveness of this approach, and most guidelines currently say more evidence is needed before pre-operative chemotherapy can be recommended.

This brief examines the evidence on pre-operative chemotherapy, including the results of a new individual participant data (IPD) systematic review and meta-analysis.

The evidence on pre-operative chemotherapy

There have been a number of systematic reviews, based on aggregate data from randomised controlled trials, looking into whether the addition of chemotherapy given before surgery improves survival for patients with NSCLC. These reviews have suggested a benefit of pre-operative chemotherapy, but the evidence from them has been weakened by the inclusion of different combinations of trials, some of which are confounded by the use of chemotherapy on both arms or radiotherapy on only one arm of the trial. This makes it difficult to interpret the specific effect of giving chemotherapy before surgery. In addition, analyses of other outcomes, e.g. recurrence, and whether the treatment effect varies by patient characteristics, were not possible with the aggregate data.

The evidence for pre-operative chemotherapy has been considerably strengthened by a new systematic review and IPD meta-analysis that includes data from 15 trials, with 92% of patients known to have been randomised in all trials looking into this question.

Individual Participant Data (IPD) Meta-analysis

Systematic reviews are used to summarise the effects of treatments based on all the available evidence from randomised trials. Meta-analyses that are based on individual patient or participant data (IPD) are a particular type of systematic review. They involve the collection of the original data from all the relevant trials worldwide. The IPD approach can improve the quality of both the data and the analyses and the reliability and robustness of the results. It also allows for assessment of any variations in the effect of a particular treatment by patient characteristics, enabling treatments to be better targeted. Therefore, the IPD approach is considered to be the gold standard of systematic review.

Key Points

- Almost 1.5 million new cases of non-small cell lung cancer (NSCLC) are diagnosed each year
- Surgery is considered the best treatment option, but at diagnosis only 20-25% of tumours are suitable for potentially curative surgery
- Two previous studies, based on IPD, have found that post-operative chemotherapy improves survival compared to surgery alone
- This IPD meta-analysis of 15 randomised controlled trials has found that pre-operative chemotherapy also improves survival compared to surgery alone, with similar treatment effects to those found with post-operative chemotherapy
- Pre-operative chemotherapy is a valid treatment option for patients with resectable NSCLC, and may be preferable to post-operative chemotherapy for those with poorer prognosis or in regions where waiting lists for surgery are longer

Survival

The study found a clear benefit of pre-operative chemotherapy, with a 5% absolute improvement in survival at five years compared to no pre-operative chemotherapy. This benefit was evident regardless of whether the patients also received post-operative chemotherapy, the number of pre-operative chemotherapy cycles patients received, the chemotherapy regimen used, and whether or not patients received post-operative radiotherapy. It was beneficial to patients regardless of their age, performance status, histology or stage. The majority of included patients were classified as stage IB, IIB and IIIA, therefore the results are most reliable for these stages.

Other outcomes

Pre-operative chemotherapy led to an absolute improvement in recurrence-free survival of 6% at 5 years. It also had an absolute improvement on time to distant recurrence of 10% at 5 years, which suggests that it may help to eradicate clinically undetectable metastases. Whilst the effect is less clear, results also indicate a potential improvement on time to local recurrence of 3% at 5 years.

Despite concerns that delays to surgery due to pre-operative chemotherapy could lead to an increased early mortality this was not observed.

Despite predictions that pre-operative chemotherapy could reduce tumour size and thus improve the rates of complete resection, there was no clear evidence of an effect of chemotherapy on complete resection rate in this study.

Whilst it was not possible to assess toxicity at the patient-level, 13 out of the 15 trials included in this study reported toxicity was mild or acceptable and the treatment was generally well tolerated.

How does this compare to post-operative chemotherapy?

Although this study was unable to directly compare the effect of pre-operative and post-operative chemotherapy, there is a similar magnitude of benefit seen with post-operative chemotherapy. One three-armed trial that included both treatment options did not have enough power to compare the two treatments directly reliably, but again, similar effects were seen with both treatment approaches.

Pre-operative chemotherapy should be regarded as a valid treatment option for patients with resectable NSCLC.

Pre-operative chemotherapy may be preferable for patients with poorer prognosis, larger tumours, or who are less likely to be able to tolerate chemotherapy after surgery, and in regions with longer waiting lists for surgery. Post-operative chemotherapy may be preferred by patients wishing to have potentially curative treatment immediately, and for those with earlier stage disease. It also allows tumours to be more accurately staged, which indicates whether post-operative chemotherapy is needed.

As pre-operative chemotherapy has a large impact on metastases and it has previously been reported that post-operative chemotherapy has an impact on distant control it is tempting to suggest a combination of pre and post operative chemotherapy may have a larger impact on survival. Further head to head comparisons of these treatments may be warranted.

CONCLUSIONS

Pre-operative chemotherapy is beneficial for people with resectable NSCLC, compared to surgery alone. It improves survival at 5 years from 40% to 45%. It also improves recurrence-free survival, with a large impact on time to distant metastases.

The benefits of pre-operative chemotherapy are similar to post-operative chemotherapy. This provides another treatment option for people with NSCLC, and could be particularly helpful to those with poorer prognoses, or facing longer waiting lists for surgery.

It is possible that a combination of both pre- and post-operative chemotherapy could have a greater impact on local and distant control and survival, but further research is needed.

To our knowledge, this is the first time pre-operative chemotherapy for patients with resectable NSCLC has been explored in a systematic review and IPD meta-analysis. Our results conclusively show that pre-operative chemotherapy is a valid treatment option for people with NSCLC.

RECOMMENDATIONS

- Pre-operative chemotherapy should be considered as a valid treatment option for patients with resectable NSCLC
- Further research on the effects of combined pre- and post-operative chemotherapy may be warranted.

RECOMMENDED READING

NSCLC Meta-analysis Collaborative Group. Pre-operative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet. 2014; doi:10.1016/S0140-6736(13)62159-5

NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small cell lung cancer: two meta-analyses of individual patient data. Lancet. 2010;375(9722):1267-77.