Online Appendix D2 BTS Guideline for Pleural Disease

Section D Pleural malignancy

Question D2 Evidence Review and Protocol

D2 For adults with malignant pleural effusion, does systemic therapy avoid the need for definitive pleural intervention?

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Question Evidence Review

D2 For adults with malignant pleural effusion, does systemic therapy avoid the need for definitive pleural intervention?

Background

Malignant pleural effusions (MPE) often recur after initial aspiration. Since MPE is a marker of advanced disease and is associated with a poor prognosis, treatment focuses on palliation of symptoms and maintenance of quality of life. The best way to achieve these outcomes in MPE is with a definitive pleural procedure, e.g. pleurodesis or insertion of an indwelling pleural catheter (IPC), performed early to reduce repeated pleural procedures. Anecdotal reports suggest that MPEs often resolve rapidly after initiation of chemotherapy, avoiding the need for a definitive procedure. The aim of this review was to determine whether systemic anti-cancer therapy reduces the requirement for pleural drainage and pleurodesis, with specific focus on treatment-sensitive tumours.

Outcome

Avoidance of the need of a definitive pleural procedure (pleurodesis, IPC insertion or surgery)

Evidence Review

Included studies

19 studies were identified as potentially relevant to this review, but none compared the need for a definitive pleural procedure in patients with MPE treated with systemic therapy versus no systemic treatment. Six studies compared one systemic therapy with another or examined alternative outcomes in the relevant patient population and were considered pertinent to the review.[1-6] Studies included MPE due to breast cancer[1,2] and MPE due to non-small-cell lung carcinoma (NSCLC)[3-6], but there was heterogeneity in the treatment regimens, which included multiple chemotherapy agents, targeted therapies and anti-angiogenesis drugs.

MPE from breast cancer

In patients with MPE from breast cancer, Mitchell et al assessed the impact of systemic oncological therapy against no systemic treatment on the removal of existing IPCs.[1] Survival was shorter in the non-treatment group and many patients died with IPCs *in situ*. The study included 55 patients receiving third-line chemotherapy and 41 patients with triple-negative receptor-status tumours, which cannot be considered “treatment-sensitive” tumours. There was a trend towards higher rates of IPC removal in patients receiving first-line chemotherapy compared with third-line chemotherapy, but the study was not powered for this sub-group analysis.

Hirata et al evaluated breast cancer patients with MPE for pleural progression-free survival (PPFS) after undergoing drainage and pleurodesis or therapeutic aspiration. Although the starting point for calculation of PPFS differed between the two arms, causing lead-time bias to affect the pleurodesis arm, 49/78 patients who received systemic treatment following simple aspiration went on to receive pleurodesis suggesting that chemotherapy alone did not control the pleural effusion.[2]

MPE from non-small-cell lung carcinoma (NSCLC)

Several studies examined the role of systemic bevacizumab in NSCLC. Masago et al reported effusion recurrence after cessation of systemic treatment in 12 of the 15 responders suggesting that systemic bevacizumab was effective in controlling pleural fluid while treatment was ongoing.[3] Jiang et al reported on patients with epidermal growth factor receptor (EGFR)-mutated NSCLC and acquired tyrosine kinase inhibitor (TKI) resistance that were treated with bevacizumab and either a continuation of EGFR-TKI or switch chemotherapy. Both complete or partial pleural effusion response and PPFS were shown to be significantly greater ($p = 0.005$ and $p = 0.042$ respectively) in the continuation EGFR-TKI group than those who switched to chemotherapy.[4] Finally, systemic bevacizumab, carboplatin and paclitaxel led to pleural effusion response rates of 91% in 23 patients with MPE due to recurrent or metastatic NSCLC.[5]

Finally, one study investigated the administration of granulocyte-cell stimulating factor (G-CSF) to a small sub-group of patients with MPE due to NSCLC and reported moderate success in controlling pleural effusions.[6]

Evidence statements

There was insufficient evidence to determine if systemic anti-cancer therapy reduces the need for definitive pleural procedures in adults with MPE.

Systemic anti-angiogenesis agents may improve pleural effusion control in NSCLC, but methodological constraints limit the interpretation of these results.

Recommendation

- Definitive pleural intervention should not be deferred until after systemic anti-cancer therapy (SACT) (**Conditional** – by consensus)

Research Recommendations

- Further research is required to describe the effect of systemic therapy in patients with MPE, specifically those with treatment-sensitive tumours such as small cell lung cancer, lymphoma and hormone receptor-positive breast cancer
- Further studies are needed to investigate the effect of systemic anti-angiogenesis agents in patients with MPE, specifically those with NSCLC and EGFR mutations

References

1. Mitchell MA, Burkett A, Li P, Zhang T, Amjadi K. Effect of chemotherapy on removal of indwelling pleural catheters in breast cancer patients with malignant pleural effusions. *Respiration.* 2018;96(6):552-559.
2. Hirata T, Yonemori K, Hirakawa A, et al. Efficacy of pleurodesis for malignant pleural effusions in breast cancer patients. *Eur Respir J.* 2011;38(6):1425-1430.
3. Masago K, Fujimoto D, Fujita S, et al. Response to bevacizumab combination chemotherapy of malignant pleural effusions associated with non-squamous non-small-cell lung cancer. *Mol.* 2015;3(2):415-419.
4. Jiang T, Li A, Su C, et al. Addition of bevacizumab for malignant pleural effusion as the manifestation of acquired EGFR-TKI resistance in NSCLC patients. *Oncotarget.* 2017;8(37):62648-62657.
5. Tamiya M, Tamiya A, Yamadori T, et al. Phase 2 study of bevacizumab with carboplatin-paclitaxel for non-small cell lung cancer with malignant pleural effusion. *Med Oncol.* 2013;30(3):676.
6. Fujita A, Takabatake H, Tagaki S, Sekine K. Combination chemotherapy in patients with malignant pleural effusions from non-small cell lung cancer : cisplatin, ifosfamide, and irinotecan with recombinant human granulocyte colony-stimulating factor support. *Chest.* 2001;119(2):340-343.

Question Protocol

Field	Content
Review Question	For adults with malignant pleural effusion, does systemic therapy avoid the need for definitive pleural intervention?
Type of review question	Intervention review
Objective of the review	To determine whether chemotherapy reduces the requirement for pleural drainage and pleurodesis
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with malignant pleural effusion
Eligibility criteria – intervention(s)	Systemic therapy
Eligibility criteria – comparators(s)	No systemic therapy
Outcomes and prioritisation	Definitive pleural intervention not needed (i.e. IPC or pleurodesis or surgery)
Eligibility criteria – study design	RCTs Prospective comparative studies Case series of >100 patients
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but **DO NOT** use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Driver mutation positive Small cell Lymphoma Ovarian
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter

	should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	RevMan5 Pairwise meta-analyses Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. Gradeprofiler Quality of evidence assessment Gradepro Recommendations
Information sources – databases and dates	MEDLINE, Embase, PubMED, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews 1966 - present
Methods for assessing bias at outcome / study level	RevMan5 intervention review template and NICE risk of bias checklist (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler Intervention review quality of evidence assessment for each outcome (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Rationale / context – what is known	For specific diseases (especially small cell lung cancer, breast and ovarian cancer), it is common practice to delay pleural intervention, if the patient is not too breathless, until systemic treatment has been given.