Online Appendix D11 BTS Guideline for Pleural Disease

Section D Pleural malignancy

Question D11 Evidence Review and Protocol

D11 For adults with pleural malignancy, is intrapleural chemotherapy better than systemic treatment at improving clinical outcomes?

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Question Evidence Review

D11 For adults with pleural malignancy, is intrapleural chemotherapy better than systemic treatment at improving clinical outcomes?

Background

Systemic anti-cancer therapy (SACT) provides the mainstay of active treatment for all patients with metastatic cancer, including those with disease spread to the pleura. Symptomatic malignant effusions can affect quality of life, breathing and performance status of these patients and hinder their ability to tolerate SACT, with drainage often needed prior to SACT commencing. Historically, some chemotherapy agents were delivered intrapleurally to act as sclerosants to aid pleurodesis. Recently, with the advent of medical thoracoscopy, regular insertion of indwelling pleural catheters (IPCs), and a growing number of novel anti-cancer treatments including immunologic and biologic agents, the intent of delivering intrapleural anti-cancer treatments has expanded beyond obtaining pleurodesis. This review investigates if intrapleural anti-cancer therapies improve clinical outcomes over systemic treatments.

Outcomes

Quality of life, length of hospital stay, need for re-intervention, symptoms (breathlessness, chest pain), complications, pleurodesis rates and mortality/survival

Evidence Review

Twenty-three studies were identified of potential relevance to the review. Recent studies generally included the use of SACT for all patients as an additional standard of care rather than as a comparator for intrapleural therapy. No studies directly compared intrapleural anti-cancer therapy with systemic anti-cancer therapy alone, but five studies were deemed relevant, and the treatment strategies are summarised in Table D11a.

Table D11a: Summary of treatment strategies across the included publications

Study	Anti-cancer therapies
Du 2013[1]	Intrapleural chemotherapy versus intrapleural combination therapy*
Groth 1991[2]	Intrapleural chemotherapy versus intrapleural sodium chloride
Jie Wang 2018[3]	Intrapleural† chemotherapy versus intrapleural† combination therapy*
Tohda 1999[4]	Intrapleural chemotherapy
Zhao 2014[5]	Intracavitary‡ chemotherapy vs intracavitary combination therapy*

* Combination therapy – chemotherapy plus vascular endothelial growth factor (VEGF)-inhibitor or angiogenesis inhibitor

† Intrapleural treatments only but described as intracavitary within the publication

‡ Mixed intrapleural and intra-abdominal

Quality of life

Three studies reported on quality of life.[1,3,5] One study compared the intrapleural administration of chemotherapy alone against chemotherapy plus vascular endothelial growth factor (VEGF)-inhibitor[1] and two studies compared intrapleural or intracavitary administration of chemotherapy alone against chemotherapy and angiogenesis inhibitor[3,5]. The latter two studies showed a significant improvement in quality of life when using combined intrapleural therapy (chemotherapy and angiogenesis inhibitor) (p = 0.011 and <0.05 respectively).[3,5] Data are summarised in Table D11b.

Length of hospital stay and need for re-intervention

No data was reported on length of hospital stay or need for re-intervention.

Table D11b: Quality of life following intrapleural and intracavitary anti-cancer treatments

Study	% Patients reporting improved quality of life (no. patients) Du 2013 [1]	Jie Wang 2018† [3]	Zhao 2014‡ [5]
Intrapleural chemotherapy	50% (15/30)	60% (37/62)	
Intrapleural combination therapy*	83% (30/36)	80% (53/66)	
Intracavitary chemotherapy			59% (13/22)
Intracavitary combination therapy*			87% (20/23)
p	Not reported	0.011	<0.05

* Combination therapy – chemotherapy plus vascular endothelial growth factor (VEGF)-inhibitor or angiogenesis inhibitor

† Intrapleural treatments only but described as intracavitary within the publication

‡ Mixed intrapleural and intra-abdominal

Quality of life measured by Karnofsky Performance status scores (KPS)[1,5], or the European Organization for Research and Treatment of Cancer quality of life questionnaire C30 (EORTC QLQ-C30)[3]

Symptoms (breathlessness, chest pain)

One study reported substantially improved breathlessness and reduced chest pain with intrapleural chemotherapy and intrapleural chemotherapy and angiogenesis inhibitor, but there was no significance between the groups (p >0.05).[3]

Complications

All studies reported on adverse events caused by the chemotherapy/combination therapy/placebo, but only one study reported on respiratory complications stating that neither intrapleural chemotherapy or intrapleural chemotherapy and angiogenesis inhibitor caused haemopneumothorax or pneumothorax from the central venous catheter inserted into the pleural cavity (both treatments were intrapleural treatments but were described as 'intracavitary' within the publication).[3]

Pleurodesis rates

Two studies reported on effusion relapse[2,3] and one study reported on effusion control[1]. A summary of the data is shown in Table D11c and Table D11d respectively. The limited data suggest improved effusion control with intrapleural combination therapies compared to intrapleural chemotherapy alone.

Table D11c: Pleural effusion relapse rate of intrapleural anti-cancer treatments

Study	Time	% Pleural effusion relapse rate Intrapleural chemotherapy	Intrapleural combination therapy*	Intrapleural 0.9% sodium chloride
Groth 1991[2]	>3 months	55%	-	67%
Jie Wang 2018[3]	<12 months	31%	10%	-

* Combination therapy – chemotherapy plus angiogenesis inhibitor

Table D11d: Pleural effusion control following intrapleural anti-cancer treatments

Study	Time	% Increased pleural effusion control Intrapleural chemotherapy	Intrapleural combination therapy*
Du 2013[1]	After first cycle	50%	83%

* Combination therapy – chemotherapy plus vascular endothelial growth factor (VEGF)-inhibitor

Mortality/survival

Survival data was reported in four studies and data are summarised in Table D11e.[1-4] Although no study directly compared intrapleural chemotherapy against systemic anti-cancer therapies, the limited data suggest that progression free survival and overall survival time may be improved with combination intrapleural treatments over intrapleural chemotherapy alone.[1,3]

Table D11e: Survival data comparisons between different intrapleural anti-cancer treatment strategies

Study	Intrapleural chemotherapy	Intrapleural combination therapy*	Intrapleural 0.9% sodium chloride	*p*
		Median overall survival time (months)		
Du 2013[1]	10.1	10.3	-	>0.05
Groth 1991[2]	5.0	-	6.0	NS
		Median progression free survival (months)		
Du 2013[1]	4.5	5.3	-	<0.05
		Mean overall survival time (months)		
Tohda 1999[4]	8.0	-	-	-
		1-year overall survival rate (% patients alive at year 1)		
Jie Wang 2018[3]	74%	79%	-	0.54

* Combination therapy – chemotherapy plus angiogenesis inhibitor or VEGF-inhibitor

NS – not significant

Evidence Statements

There was no direct evidence to support this question; and based on very limited evidence:

Intrapleural combination therapies (chemotherapy plus vascular endothelial growth factor (VEGF)-inhibitor or angiogenesis inhibitor) may improve effusion control and increase quality of life, progression free survival and survival time when compared with chemotherapy alone (**Ungraded**)

Recommendation

- Intrapleural chemotherapy should not be routinely used for the treatment of malignant pleural effusion (**Conditional** – by consensus)

Good Practice Point

- ✓ All patients of good performance status with metastatic malignancy should be considered for systemic anti-cancer therapy as standard of care as per national guidelines

Research Recommendation

- Research is needed into assessing the clinical effects of novel intrapleural anti-cancer agents in combination with standard care systemic anticancer treatment for the treatment of adults with pleural malignancy

References

1. Du N, Li X, Li F, et al. Intrapleural combination therapy with bevacizumab and cisplatin for non-small cell lung cancer-mediated malignant pleural effusion. *Oncol Rep.* 2013;29(6):2332-2340.
2. Groth G, Gatzemeier U, Haussingen K, et al. Intrapleural palliative treatment of malignant pleural effusions with mitoxantrone versus placebo (pleural tube alone). *Ann Oncol.* 1991;2(3):213-215.
3. Jie Wang X, Miao K, Luo Y, et al. Randomized controlled trial of endostar combined with cisplatin/ pemetrexed chemotherapy for elderly patients with advanced malignant pleural effusion of lung adenocarcinoma. *Journal of BUOn.* 2018;23(1):92-97.
4. Tohda Y, Iwanaga T, Takada M, et al. Intrapleural administration of cisplatin and etoposide to treat malignant pleural effusions in patients with non-small cell lung cancer. *Chemotherapy.* 1999;45(3):197-204.
5. Zhao WY, Chen DY, Chen JH, Ji ZN. Effects of intracavitary administration of Endostar combined with cisplatin in malignant pleural effusion and ascites. *Cell Biochemistry & Biophysics.* 2014;70(1):623-628.

Question Protocol

Field	Content
Review Question	For adults with pleural malignancy, is intrapleural chemotherapy better than systemic treatment at improving clinical outcomes?
Type of review question	Intervention review
Objective of the review	To compare outcomes for intrapleural versus systemic oncological treatment in pleural malignancy
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with pleural malignancy
Eligibility criteria – intervention(s)	Intrapleural chemotherapy
Eligibility criteria – comparators(s)	Systemic treatment (oncology)
Outcomes and prioritisation	Quality of life Length of hospital stay Need for re-intervention Symptoms (breathlessness, chest pain) Complications Pleurodesis rates Mortality / survival
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	Mesothelioma Non-mesothelioma

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	When the previous BTS Pleural Disease Guideline 2010 was published, there was little evidence available on this topic, so the question will explore if there is new data available