LONDON CANCER
NORTH AND EAST

London Cancer

Mesothelioma Lung Protocols

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Contents

1. Staging

The most commonly used system for staging mesothelioma is the TNM system: http://www.cancer.org/cancer/malignantmesothelioma/detailedguide/malignant-mesothelioma-staging

The most important prognostic factors (predicting for a better prognosis) are: female gender; epithelioid subtype; normal (not low) Hb; normal (not high) white cell count and/or platelet count. Some patients with minimal disease volume and good performance status may be considered for radical surgery in the case of isolated pleural disease and/or within the context of the MARS2 trial.

In practice a simpler method uses PET-CT to determine whether the disease is potentially resectable or not. Biomarkers are also being developed to improve on current staging and prognostic methods.

2. Mesothelioma – Summary of Chemotherapy Protocols

****Whenever possible ALL patients with mesothelioma should be considered for trials****
Antiemetics are given with the protocols below following the Pan London Anti-emetic Guidelines 2010 written by Pinkie Chambers and Susanna Daniels.

	Current disease status	Treatment regimen
A	• **Pleural or peritoneal[a] disease** good performance status, epithelioid histology, limited disease volume 1st Line Treatment	**Consider radical surgery**; **1st Line** **Pemetrexed with cisplatin (or carboplatin exceptional patients)** Pemetrexed 500mg/m^2 IV + Cisplatin 75mg/m^2 IV -Every 3 weeks for up to six cycles. Most patients will receive four cycles. - Reassess by CT scan after every two cycles. **OR** Pemetrexed 500mg/m^2 IV + Carboplatin AUC5 (EDTA) or AUC6 (CrCl) IV -Every 3 weeks for up to six cycles. Most patients will receive four cycles. - Reassess by CT scan after every two cycles. Ensure all patients have received folic acid 400 micrograms once daily and Vitamin B12 1mg intramuscularly every 9 weeks starting 1-2 weeks prior to cycle 1 and to continue throughout treatment.
B	• **Pleural or Peritoneal relapsed disease**	**Relapsed disease** **IPM PS 0-1 patients** *Day 1* Mitomycin C 6mg/m^2 IV (cycles 1 to 4 only) Irinotecan 70mg/m^2 IV Cisplatin 40mg/m^2 IV *Day 15* Irinotecan 70mg/m^2 IV Cisplatin 40mg/m^2 IV Every 28 days for four cycles. - evaluate after each 2 courses –Up to six cycles can be given in select patients - Occasionally initial dose of Irinotecan (and on subsequent cycles) can be increased to 100mg/m^2 (consultant decision) **OR** **Intravenous Vinorelbine weekly,** **PS 1-2 patients** *Two dosing schemes exist:* • Vinorelbine 30mg/m^2 (max 60mg) weekly for 6 weeks-this comprises one cycle. This is repeated for up to 6 cycles • Vinorelbine 30mg/m^2 (max 60mg) on Day one and day 8, every 21 days. For up to 6 cycles

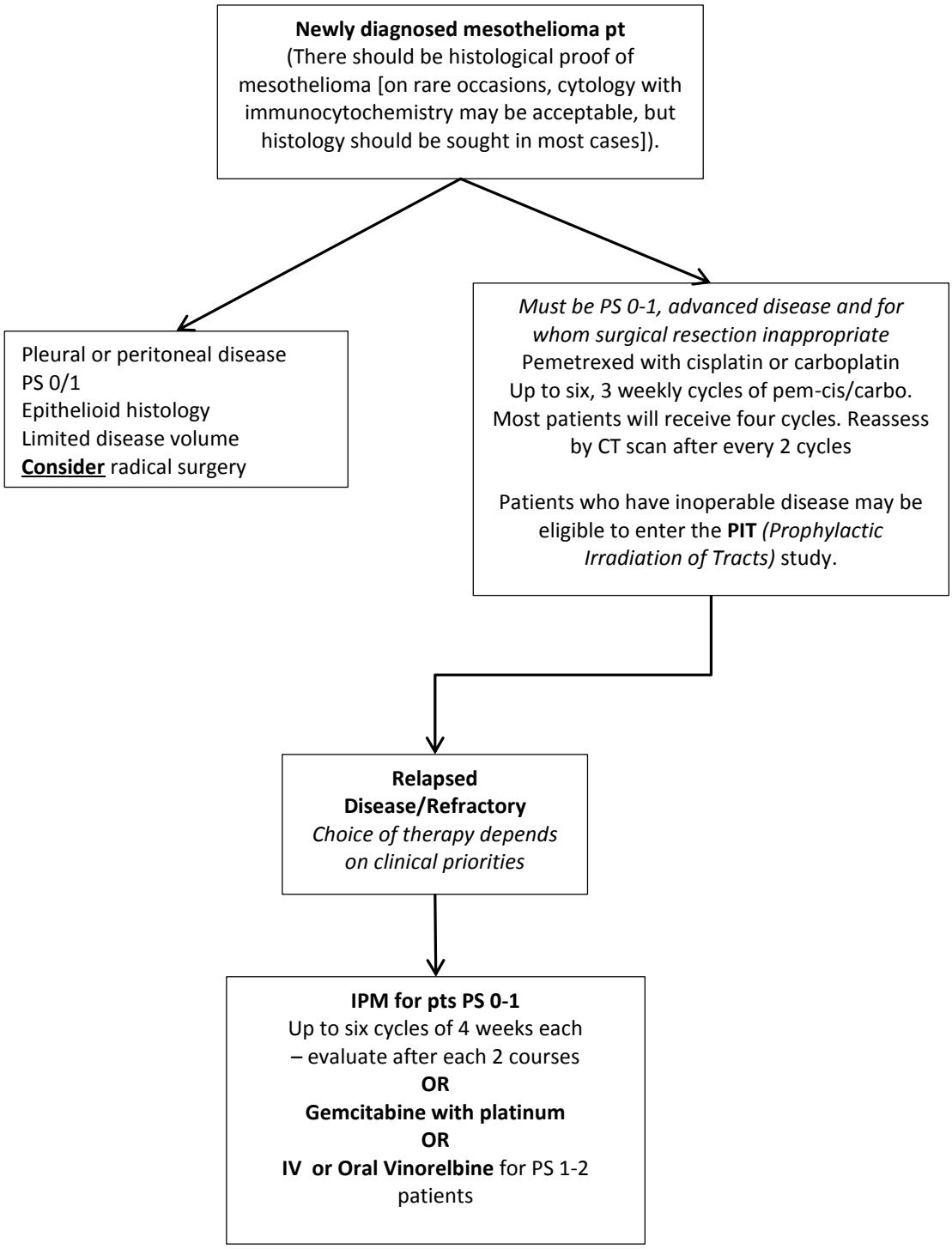
		OR **Gemcitabine + Carboplatin** *Day 1* Gemcitabine 1250mg/m^2 Carboplatin AUC5 (EDTA) or AUC 6 (CrCl) *Day 8* Gemcitabine 1250mg/m^2 Every 21 days for 4-6 cycles **OR** **Gemcitabine+Cisplatin** Cisplatin 75mg/m2 IVI day 1 Gemcitabine 1250mg/m^2 IVI days 1 and 8 Repeat every 21 days for up to 4 cycles **OR** **Oral Vinorelbine** Vinorelbine PO 60mg/m^2 D1 and D8 every 21 days Increasing if tolerated to 80mg/m^2 D1 and D8 from cycle 2 onwards.

All treatments – Histologically-confirmed malignant mesothelioma

- Adequate haematological reserve and adequate renal function
- Patient information and consent
- See protocols for drug schedule and dose modification details

[a]Please note NICE guidance strictly does not apply for peritoneal mesothelioma. An ICDFR application may be required.

Chemotherapy Plan/Algorithm for Pleural or Peritoneal Mesothelioma Patients



3. Mesothelioma Chemotherapy Protocols

3.1. Pemetrexed (Alimta®) and Cisplatin or Carboplatin ('pem-cis' or 'pem-carbo') in previously untreated pleural or peritoneal malignant mesothelioma.

Ref: Vogelzang NJ, Rusthoven JJ, et al. J Clin Oncol. 2003:21:2636-44.

NICE TA135[a] (August 2008). Pemetrexed for the treatment of malignant pleural mesothelioma.

Pemetrexed is recommended as a treatment option for malignant pleural mesothelioma only in people who have a World Health Organization (WHO) performance status of 0 or 1, who are considered to have advanced disease and for whom surgical resection is considered inappropriate.

[a]Please note NICE guidance strictly does not apply for peritoneal mesothelioma. An ICDFR(individual cancer drugs funding request) may be required.

Eligibility (main criteria)	• Histological evidence of malignant mesothelioma. • Age over 18. • Performance status 0-1 (ECOG). • Adequate haematological status (i.e. ANC ≥1.5 , platelets ≥100 and Hb ≥9) [may be transfused]. • Creatinine clearance or EDTA clearance ≥ 50ml/min (Cockroft or EDTA) • Written informed consent.
Treatment	Day 1 – Pemetrexed 500mg/m^2, Cisplatin 75mg/m^2 OR Carboplatin AUC 6 (CrCl) or AUC5 (EDTA) Repeated every 21 days for up to SIX cycles. Most patients will receive 4 cycles.
Supportive Care	Day minus 15 to 8 (i.e. one to two weeks prior to first chemotherapy cycle 1) – Folic acid, 400 micrograms orally once daily Vitamin B12, 1mg intramuscular, one dose repeated every 9 weeks
Dose modifications	If life-threatening infection occurs, reduce all doses by 20% on subsequent cycles.
Follow-up	Assessment of response made by sequential CT scanning in conjunction with clinical evaluation every two cycles

3.2. Irinotecan, Cisplatin and Mitomycin (IPM) in relapsed/refractory malignant pleural or peritoneal mesothelioma.

Ref: Fennell DA et al. Efficacy and safety of first- or second-line irinotecan, cisplatin, and mitomycin in mesothelioma. Cancer. 2007 Jan 1;109(1):93-9.

Eligibility	• Histological evidence of malignant mesothelioma (pleural or peritoneal) • Age over 18. • Performance status 0-2 (ECOG). • Adequate haematological status (i.e. WBC >3, platelets >100 & Hb >10) {may be transfused}. • Creatinine clearance or EDTA clearance >50ml/min • Written informed consent. • No history of inflammatory bowel disease, severe diarrhoea or stomach cramps not thought to be due to the tumour. • No concurrent malignancy other than non-melanoma skin cancer. • Not currently in any other investigational drugs study.
Treatment	*Day 1* - Irinotecan 70 or 100mg/m2, Cisplatin 40mg/m2, Mitomycin 6mg/m2 *Day 15* – Irinotecan 70 or 100mg/m2, Cisplatin 40mg/m2 Discuss initial irinotecan dose with consultant. Repeat whole programme every 28 days for 4 cycles. Assessment will be made after 2 and 4 cycles. If cycles 5 and 6 are to be administered, **omit** Mitomycin.
Supportive Care	Loperamide to treat chemotherapy induced diarrhoea.
Dose modifications	If life-threatening infection occurs, reduce all doses by 20% on subsequent cycles.
Follow-up	Assessment of response made by sequential CT scanning in conjunction with clinical evaluation.
Reporting serious adverse events	Any event that: results in death, is life-threatening, is permanently disabling, requires or prolongs hospitalisation or is an overdose (defined as 25% per dose or greater increase over the protocol specified dose or more doses being given in a cycle) - should be reported to Dr Rudd for adverse event reporting.

3.3. Vinorelbine – Weekly off-trial (pleural/peritoneal)

Ref: Steele JP, Shamash J, Evans MT, et al. J Clin Oncol. 2000;18:3912-7.

Eligibility	• Histological evidence of malignant peritoneal or pleural mesothelioma. • Performance status 0-2 or higher (ECOG). • Adequate haematological status (i.e. WBC >4, platelets >100 & Hb >10). • Adequate hepatic and renal function (i.e. alkaline phosphatase <1.5xULN). • Written, informed consent. • No uncontrolled cardiac or hepatic disease. • No evidence of active infection requiring antibiotic therapy. • No concurrent malignancy.
Treatment	Vinorelbine will be administered at a dose of 30mg/m2 every 7 days (max 60mg). Each cycle consists of 6 weeks. Treatment may be delivered on days 1 and 8 of a 21 day cycle. Treatment will be continued until disease progression or toxicity indicate cessation would be in the patient's best interests.
Dose modifications	If the total WBC <3, or ANC <1, or platelets <100 the next dose will be delayed by one week. The delay will be repeated if the criteria are not met the following week.
Follow-up	Response will be assessed by CT scan at: baseline, after every 6 weeks of treatment, 4 weeks after last cycle and 3-monthly thereafter until disease progression.

3.4. Gemcitabine Carboplatin

Ref: Favaretto AD, Aversa SM, Paccagnella A, et al. Cancer. 2003 Jun 1;97(11):2791-7

Eligibility	• Histological evidence of malignant peritoneal or pleural mesothelioma. • Performance status 0-2 or higher (ECOG). • Adequate haematological status (i.e. WBC >4, platelets >100 & Hb >10). • Adequate hepatic and renal function (i.e. alkaline phosphatase <1.5xULN). • Written, informed consent. • No uncontrolled cardiac or hepatic disease. • No evidence of active infection requiring antibiotic therapy. • No concurrent malignancy.
Treatment	*Day 1* Gemcitabine 1250mg/m^2 IV and Carboplatin AUC5 (EDTA) or AUC 6 (CrCl) IV *Day 8* Gemcitabine 1250mg/m^2 IV Every 21 days for 4-6 cycles
Dose modifications	If the total WBC <3, or ANC <1, or platelets <100 on D1 the next dose will be delayed by one week. On D8 if the haematological targets are not met the dose of gemcitabine may be omitted. The delay will be repeated if the criteria are not met the following week.
Follow-up	Response will be assessed by CT scan at: baseline and after every 2 cycles of treatment.

3.5. Gemcitabine Cisplatin

Ref: Catagneto B, Zai S, Dongiovanni D, Muzio A, Bretti S, Numico G, Botta M, Sinaccio G. Am J Clin Oncol. 2005 Jun;28(3):223-6.

Eligibility	• Histological evidence of malignant peritoneal or pleural mesothelioma. • Performance status 0-2 or higher (ECOG). • Adequate haematological status (i.e. WBC >4, platelets >100 & Hb >10). • Adequate hepatic and renal function (i.e. alkaline phosphatase <1.5xULN). • Written, informed consent. • No uncontrolled cardiac or hepatic disease. • No evidence of active infection requiring antibiotic therapy. • No concurrent malignancy.
Treatment	*Day 1* Gemcitabine 1250mg/m^2 IV and Cisplatin 75mg/m2 *Day 8* Gemcitabine 1250mg/m^2 IV Every 21 days for 4-6 cycles
Dose modifications	If the total WBC <3, or ANC <1, or platelets <100 on D1 the next dose will be delayed by one week. On D8 if the haematological targets are not met the dose of gemcitabine may be omitted. The delay will be repeated if the criteria are not met the following week.
Follow-up	Response will be assessed by CT scan at: baseline and after every 2 cycles of treatment.

3.6. Oral Vinorelbine

Eligibility	• Histological evidence of malignant peritoneal or pleural mesothelioma. • Performance status 0-2 or higher (ECOG). • Adequate haematological status (i.e. WBC >4, platelets >100 & Hb >10). • Adequate hepatic and renal function (i.e. alkaline phosphatase <1.5xULN). • Written, informed consent. • No uncontrolled cardiac or hepatic disease. • No evidence of active infection requiring antibiotic therapy. • No concurrent malignancy.
Treatment	Vinorelbine 60mg/m^2 once on D1 and D8 repeated every 21 days. Dose is increased on cycle 2 to 80mg/m^2 if neutrophils remain >1x10^9/l
Dose modifications	If neutrophil count >1.5x 10^9/l and platelets >100x10^9/l then dose can be given at 100%.

	If neutrophils 1.0-1.49x10^9/l OR platelets 75-99x10^9/l then dose should be reduced by 25%. If neutrophils <1.0x10^9/l or <100x10^9/l then dose should be delayed or omitted. If at any point neutrophils drop to <0.5x10^9/l delay until recovery then dose reduce to 60mg/m^2 from that point onwards.
Follow-up	Response will be assessed by CT scan at: baseline and after every 2 cycles of treatment.

4. APPENDIX Table A: Flowchart of the Schedule of Assessments for Palliative Treatment of Mesothelioma

The following bloods should be met on D1 of each cycle of treatment unless specified otherwise in the tables below or elsewhere in the protocol book. The decision to treat or confirm a treatment outside of these recommendations should be discussed with the Specialist Oncology Registrar or Consultant:

WCC ≥3.0 Neuts ≥1.0 Plt≥100 LFTs < ULN
Cr <10% increase from baseline Cr if receiving platinum otherwise Cr< ULN

Regimen	Pemetrexed/ Cisplatin	Pemetrexed/ Carboplatin	IPM		IV Vinorelbine						Gemcitabine/Carboplatin	
Intent	Palliative	Palliative	Palliative		Palliative						Palliative	
Cycle	C1-6	C1-6	C1-6		C1-6						C1-4	
Day	D1	D1	D1	D15	D1	D8	D15	D22	D29	D36	D1	D8
CT	Pre- treatment and after every 2 cycles				Pre-treatment and after every cycle						Pre- treatment and after every 2 cycles	
PET-CT	Not routinely done but may be required in some patients.											
Complete physical examination (inc height)	Examination before treatment- after that only when clinically indicated											
Performance Status	✓	✓	✓	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓	N/A
Weight (only recalculate BSA when >10% diff from baseline)	✓	✓	✓	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓	N/A
Haematological parameters[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Biochemistry[2, 4]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Liver Function Tests[3,4]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Regimen	Gem/Cisplatin		Oral Vinorelbine	
Intent	Palliative		Palliative	Palliative
Cycle	C1-6		C1-6	
Day	D1	D8	D1	D8
CT	Pre- treatment and after every 2 cycles			
PET CT	Not routinely done but may be required in some patients			
Complete physical examination (inc height)	Examination before treatment- after that only when clinically indicated			
Performance Status	✓	N/A	✓	N/A
Weight (only recalculate BSA when >10% diff from baseline)	✓	N/A	✓	N/A
Haematological parameters[1]	✓	✓	✓*	✓*
Biochemistry[2, 4]	✓	✓	✓	✓
Liver Function Tests[3,4]	✓	✓	✓	✓

*** Please note different neutrophil target for oral vinorelbine. If neutrophil count >1.5x 109/l and platelets >100x109/l then dose can be given at 100%. Please refer to protocol for full information.**

Table Footnotes

1. WBC, Haemoglobin, Platelets, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
2. Sodium, Potassium, BUN, Cr, Calcium, Albumin, Phosphorus
3. Bili, ALT, ALP
4. Dose reductions to chemotherapy drugs in the protocols will be applied as described in the North London Cancer Network "Dosage Adjustment for Cytotoxics in Hepatic Impairment-January 2009" and Dose Adjustment for Cytotoxics in Renal Impairment-January 2009"