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Evidence-based Series #7-14-1: Section 1

The Use of Chemotherapy in Patients with Advanced Malignant Pleural Mesothelioma: A Clinical Practice Guideline

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Questions

1. In patients with advanced malignant pleural mesothelioma, does palliative chemotherapy improve quality of life or symptom control?
2. In patients with advanced malignant pleural mesothelioma, does palliative chemotherapy improve survival?
3. Which chemotherapeutic agents (or combinations of agents) have shown the highest response rates?

Target Population

The recommendations apply to adult patients with advanced, symptomatic malignant pleural mesothelioma who have a good performance status (Eastern Cooperative Oncology Group 0-1) and are not suitable for surgical resection.

Recommendations and Key Evidence

Despite many reports on the use of chemotherapy in the palliative treatment of malignant pleural mesothelioma, only a limited amount of high-quality evidence exists on which to base recommendations. Based on this limited evidence, the Lung Cancer Disease Site Group offers the following opinions:

- **Pemetrexed 500 mg/m² and cisplatin 75 mg/m² every 3 weeks, with vitamin supplementation with B₁₂ 1000 µg monthly and folic acid 0.4-1.0 mg daily is recommended for the palliative treatment of adult patients with advanced malignant pleural mesothelioma. Both vitamin supplements should be started before the administration of pemetrexed.**
- **If pemetrexed is not available, there is evidence from a smaller trial (n=250) to recommend the use of raltitrexed 3 mg/m² and cisplatin 80 mg/m² every three weeks. This trial found a significant survival difference (p=0.0483) and the hazard ratio for the raltitrexed trial was very similar to that of the pemetrexed trial (HR 0.76 versus HR 0.77, respectively). However, response rate and progression-free survival did not achieve conventional statistical significance in the raltitrexed trial.**

Key Evidence

- One large randomized trial comparing chemotherapy with pemetrexed 500 mg/m² and cisplatin 75 mg/m² every three weeks to cisplatin alone demonstrated improved survival and quality of life for the two-drug combination versus single-agent cisplatin. That trial included 448 eligible patients randomized to either single-agent cisplatin or the combination regimen. Response rates (41% versus 17% respectively, p<0.001), time to progression (5.7 versus 3.9 months, p=0.001), and survival (12.1 versus 9.3 months, hazard ratio 0.77, p=0.020) all favoured combination treatment. Grades 3 and 4 toxicity were higher with the combined treatment: neutropenia (28% versus 2%), thrombocytopenia (6% versus 0%), vomiting (13% versus 4%), and febrile neutropenia (2% versus 0%). Two quality-of-life indices (dyspnea and pain) assessed using the Lung Cancer Symptom Scale were significantly improved with pemetrexed and cisplatin after six cycles of treatment (p=0.004 and p=0.017, respectively).
 - A second trial randomised 250 patients to either raltitrexed plus cisplatin, versus cisplatin alone. This trial demonstrated a significant improvement in survival (11.4 versus 8.8 months, HR=0.76, p=0.0483). This trial also showed a higher response rate (23.6% versus 13.6%, p=0.056) and longer progression free survival (5.3 versus 4 months, HR=0.78, p=0.058), although these differences did not achieve conventional statistical significance.
 - Currently there is no direct evidence to support or refute whether chemotherapy extends survival or improves quality of life as there are no trials comparing chemotherapy to best supportive care. However, the opinion of the Lung Cancer Disease Site Group is that single-agent cisplatin, the control arm for both the randomized trials, is unlikely to reduce survival in this patient population. Thus, the opinion of the Lung Cancer Disease Site Group is that the above trials provide sufficient indirect evidence that pemetrexed and cisplatin combination chemotherapy will improve survival and quality of life for these patients, and is therefore, recommended.
 - One hundred eleven noncomparative phase II trials were identified that examined chemotherapy for patients with malignant pleural mesothelioma. The pooled response rates for trials examining platinum-containing regimens as single agents (14.3%, 9 trials) or in combination with other agents (24.9%, 19 trials) are higher than the pooled response rates for trials examining non-platinum-containing regimens as single agents (3.6% to 9.0%, 51 trials) or in combination (10.4%, 12 trials).
- **The routine substitution of carboplatin for cisplatin is not recommended.**

Key Evidence

- Data from eight noncomparative phase II trials indicate that the pooled response rates to single-agent carboplatin are less than cisplatin (10.1% versus 20.0%).
- **Given the limited amount of high-quality evidence on the role of chemotherapy in malignant pleural mesothelioma, patients should be encouraged to participate in clinical trials of treatment for this disease.**

Key Evidence

- The participation of this group of patients in clinical trials is important as the absence of adequately powered clinical trials has contributed to the limited evidence about treatment benefits for malignant pleural mesothelioma to date.

Related Guidelines

- Evidence Summary Report #7-14-2: *Surgical Management of Malignant Pleural Mesothelioma.*
- Evidence Summary Report #7-14-3: *The Role of Radiation Therapy in Malignant Mesothelioma of the Pleura*

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