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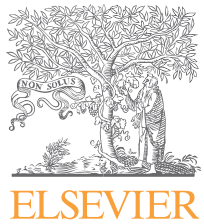

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Treatment for non small cell lung cancer, small cell lung cancer and pleural mesothelioma within the EORTC Lung Cancer Group: past, present and future

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ABSTRACT

The EORTC Lung Cancer Group (LCG) maintains a multidisciplinary clinical trial portfolio. Over the years research has moved from investigators' ideas, to pharmacological company driven studies of new drugs, to the more recent biological marker driven studies. Non-small cell lung cancer (NSCLC) is the most common malignancy and has been the area of greatest activity. Malignant pleural mesothelioma (MPM) is a rare, aggressive tumor with a poor prognosis which has been a surprising area of collaborative research in the LCG for many years. Small cell lung cancer (SCLC) is well named, as it has become 'small' in every way, and has changed from being the most hopeful of tumors to what has now become a trialist's despair. This review will provide a review of major clinical trials and the contribution of the LCG. Challenges and priorities in the way forward will be presented and discussed.

1. Non-small cell lung cancer

Many things have changed in the history of non-small cell lung cancer (NSCLC) over the past 50 years. Much of it has been summarized in the special issue of the *European Journal of Cancer* commemorating the 40-year anniversary of the EORTC,[1] and therefore we concentrate here on the past ten years in detail. We are still faced with only about 10% of patients having curative resection, and only about 20% having treatment with radical intent. Both of these areas have been important to the EORTC Lung Cancer Group (LCG) and involve a multidisciplinary approach to management – which is progress in itself. The LCG has been involved in neoadjuvant and adjuvant studies and has collaborated with other European trial groups. This has brought us to the established role of adjuvant therapy, the acceptance of neoadjuvant treatment, and the development of presurgery as a 'window' for testing new treatments. Stage III disease was the area of a major innovative trial which allowed us a number of investigational opportunities. In EORTC trial 08958, a number of different chemotherapy regimens were used pre-radical local therapy and have all been published.[2] In EORTC trial 08941 randomization was done after chemotherapy and the trial compared radical surgery to radical radiotherapy, showing that the two treatment options were equivalent

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Table 1 – EORTC phase II trials in mesothelioma

EORTC Trial	Year activated	Patients	Chemotherapy	Response rate (%)	Median OS (days)	Median PFS (days)
08976	1998	30	Temozolomide [13]	4	196	116
08966	1997	25	Caelyx [14]	7	367	167
08943	1995	25	Gemcitabine [15]	7	240	162
08924	1993	14	Paclitaxel [16]	0	273	98
08901 [a]	1992	14	Etoposide [17]	7	243	107
				5	206	101
08864	1986	14	Epirubicin [18]	13	276	144
08852	1984	46	Mitoxantrone [19]	3	237	124
08992	1999	24	Raltitrexed [20]	25	213	192

[a] Two phase II trials.

but had different toxicity spectrums. [3] The unanswered question now is if three modalities are better than two.

However, most lung cancer is advanced, and treatment is palliative, and the most frequently used palliative regimen worldwide is carboplatin and paclitaxel. This regimen was the investigational arm of a phase III study at the EORTC with comparison to the then standard of cisplatin and tenioposide, and these data were used for the registration of this combination. [4] Since then much work has been done on the number of cycles, the role of maintenance therapy, and the definition of subgroups with mutations which predict both a better prognosis and a different treatment pathway. The LCG is currently conducting a switch maintenance study, EORTC 08092, with pazopanib and actively looking at the role of radical treatment in subgroups with mutations.

2. Malignant mesothelioma

The etiology, epidemiology, diagnosis, prognosis and management of malignant pleural mesothelioma (MPM) have recently been reviewed and guidelines have been issued. [5] Essential prognostic factors associated with better outcome are earlier stage and epithelioid histologic type as described by the LCG and other groups. [6] Additional bad prognostic factors are the presence of symptoms, poor performance status, advanced age, male gender, elevated white blood cell count (WCC) and platelets, and weight loss. The prognostic value of asbestos exposure is not proven.

Radical surgery in MPM remains controversial. Operative mortality has fallen to an acceptable level of around 5% in experienced centers, but morbidity remains high at around 50%. [7,8] In the EORTC phase II trial 08031, administration of three modalities (chemotherapy, surgery, and radiotherapy) was only possible in 42% of patients within the proposed ideal time of 90 days. The median survival was 33 months in the 37 patients receiving tri-modality treatment. [9] Although the multimodality treatment procedure seems feasible, overall treatment time is long, and psychological distress is considerable. These findings stress the importance of and the need for a large prospective multicenter trial in which operable patients with early-stage resectable MPM are randomly assigned to a surgical and a non-surgical management. [10] The feasibility of this approach has been explored in the UK MARS trial in which the randomization was between extrapleural pneumonectomy (EPP) followed by post-operative radiotherapy (PORT) and any palliative treatment, including pleurodesis, following an induction treatment with chemotherapy for all patients. The results of the feasibility part of this trial have recently been released and show no difference in survival between treatment arms [11,12] thereby questioning the appropriateness of EPP as surgical approach in MPM. Further trials in this disease are necessary and remain on the LCG agenda.

Although rare cases of complete response have been reported with systemic chemotherapy, the aim of chemotherapy is primarily palliation, and unlike surgical cases, few anecdotes are present in the literature (although many oncologists have seen impressive durable responses). In the past decades many phase II studies have been performed to select drugs with a potential activity against MPM, and Table 1 summarizes the EORTC experience. [13–20] A three-arm randomized phase III study was initiated in the United Kingdom that compared the efficacy of two different chemotherapy regimens, one low-dose platinum combination and one single-agent third generation drug, with best supportive care. [21] The study was prematurely stopped due to slow accrual and was hence insufficiently powered to show a survival difference even after pooling the results of both chemotherapy arms. However, a positive trend favoring the vinorelbine single-agent treatment was observed. Still, the choice of the comparative chemotherapy is not considered optimal.

The promising results obtained in previous phase I and II trials with raltitrexed led to a phase III trial, EORTC 08983, conducted by the LCG designed to determine whether first-line treatment with raltitrexed,