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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,

a thymidine synthase inhibitor, and cisplatin results in superior outcome compared with cisplatin alone in patients with MPM. [22] Patients with histologically proven advanced MPM, chemo-naive, WHO performance status 0 to 2, and adequate hematological, renal, and hepatic function were randomly assigned to receive cisplatin (80 mg/m^2 IV) on Day 1, either as single agent or combined with raltitrexed (3 mg/m^2).

Two hundred fifty patients were randomized. There were no toxic deaths, and the main grade 3 or 4 toxicities observed were neutropenia and emesis which were reported twice as often in the combination arm. Among 213 patients with measurable disease, response rate was 13.6% with cisplatin *versus* 23.6% for the combination ($P = 0.056$). No difference in health-related quality of life (HRQOL) was observed on any of the scales. However, it is clear that both groups had impairment of global HRQOL scores, when compared to a normative general population. Importantly, in this disease population, this level did not deteriorate, remaining stable over treatment time.

Median overall survival was 8.8 months for cisplatin (95% confidence interval [CI] 7.8–10.8) *versus* 11.4 months (95% CI 10.1–15) for the combination, and 1-year survival was 40% *versus* 46%, respectively ($P = 0.048$). Based on these results it can be concluded that the combination of raltitrexed and cisplatin improves overall survival (OS) and is superior compared to cisplatin alone without harmful effect on HRQOL. These results are comparable to the results obtained in the other randomized phase III EMPHACIS-trial of cisplatin alone *versus* cisplatin combined with pemetrexed in patients with MPM conducted around the same time. [23] Although the significance level in the EORTC raltitrexed study is somewhat less than in the EMPHACIS-trial, this could be the result of its lower sample size. The magnitude of the observed improvement in the combination arms – as expressed by the hazard ratio – and the outcome in both control arms are similar, making these trials comparable and confirmatory of each other. This equipoise is confirmed by an adjusted indirect comparison of response rate (odds ratio [OR] 0.56, 95% CI 0.24–1.30), progression-free survival (PFS) (OR 1.15, 95% CI 0.82–1.61) and OS (OR 0.99, 95% CI 0.69–1.41).The cost-effectiveness analysis found raltitrexed plus cisplatin to be cost-effective at a cost per quality adjusted life year of £11,425 compared to cisplatin and £25,331 compared to Active Supportive Care. [24] These data have led to the recent registration of raltitrexed for the treatment of MPM in several European countries. Based on these two randomized phase III trials, it is now generally accepted to treat patients with MPM with a combination of an antifolate with platinum.

Recent pharmaceutical developments have focused on the identification and inhibition of molecular pathways involved in the growth and progression of MPM. A number of novel agents have been or are being evaluated including drugs targeted against epidermal growth factor, platelet-derived growth factor, vascular endothelial growth factor, src kinase, histone deacetylase, proteosome, and mesothelin. [25–27] Of these approaches, thalidomide is negative. [28] Bevacuzimab is still being tested with a platinum pemetrexed combination using a biomarker generated from the previous bevacuzimab study. [29,30] Sorafenib appears interesting and more data will be available soon. [31,32] Bortezomib appears very active and is the current focus of the LCG with a program of tissue collection, EORTC trial 08052, to look at biological pathways involved in drug resistance to this and other agents. [33] A randomized second-line trial is comparing best standard of care with and without a new molecular NGR-hTNF which should deliver tumor necrosis factor via targeting vessels. [34] The LCG is proud to have been able to harness interest from many centers in many countries to recruit patients with this rare disease.

3. Small cell lung cancer

The backbone of treatment for small cell lung cancer (SCLC) is chemotherapy. Standard treatments remain platinum- or anthracycline-based and have changed little over the past ten years. The most recent first-line contender has been amrubicin, a third generation synthetic anthracycline agent which does not appear to cause anthracycline-related cardiomyopathy. It has shown comparable response rate as a single agent (61%) to cisplatin/etoposide (63%) and a promising response of 77% in combination with cisplatin (EORTC trial 08062). [35] Toxicity was largely myelosuppression in all three arms. New combinations in SCLC must show a survival advantage over cisplatin/etoposide unless there is a significantly different toxicity profile.

Sunitinib, a multi-targeted inhibitor of VEGFR-1/2/3, PDGFR alpha/beta, Flt 3, c-kit, and RET, has been developed as monotherapy in second-line treatment for relapsed or refractory SCLC. Sunitinib has anecdotally given responses in this EORTC second-line study, EORTC trial 08061, which have been confirmed by PET scanning. This trial was slow to recruit, is complex in design, and challenges future design of this type of study within a cooperative group.

Brain metastases are frequent in SCLC and are associated with serious impairment in quality of life and shortened survival. The EORTC has led the way in the prevention of brain metastasis with results that have made a real impact on the management of SCLC and have prolonged survival. Two clinical trials evaluating prophylactic cranial irradiation (PCI) have been conducted by the LCG and the EORTC Radiation Oncology Group in the last decade (EORTC trials 22003–08004 and 22993–08993). The impact of PCI on the

incidence of brain metastasis, OS, and quality of life was evaluated.

EORTC trial 22993/08993 is the only study ever conducted to establish the role of PCI in stage IV SCLC (or extensive-stage SCLC). Historically, in stage IV SCLC radiotherapy has always had a role in the palliation of symptoms but no proven impact on survival. This EORTC-led study compared PCI to no further therapy in 286 patients who had responded to chemotherapy. [36] The most common regimen prescribed was 20 Gy in 5 fractions followed by 30 Gy in 10 fractions. PCI resulted in a significant reduction in the risk of symptomatic brain metastases (HR 0.27, 95% CI 0.16–0.44; $p < 0.001$) and doubled the one-year survival (27.1%, 95% CI 19.4–35.5 in the PCI group and 13.3%, 95% CI 8.1–19.9 in the control group). The quality of life analysis of the study showed that the irradiated group had more prolonged hair loss and increased fatigue. [37] The mean global health status score was 8 points higher in the PCI group at 6 weeks ($p = 0.018$) and 3 months ($p = 0.056$). However, these observed differences were below the cut-off of a 10-point difference for clinical significance. As a result of this study, PCI was rapidly adopted internationally as a new standard treatment.

The second study, EORTC trial 22003–08004, in stage I–III SCLC (or limited-stage SCLC), addressed the question of the standard dose of prophylactic radiation to be delivered to the brain. [38] A meta-analysis demonstrated a significant reduction in brain metastasis and an improvement in OS with PCI [39] and suggested that higher doses of PCI may be associated with a reduction in the incidence of brain metastases. In this intergroup study (Intergroupe Francophone de Cancérologie Thoracique and EORTC) 720 patients with stage I–III SCLC in complete remission after chemotherapy and thoracic radiotherapy were randomly assigned to a standard (25 Gy) or higher (36 Gy) PCI total dose delivered using either conventional or accelerated hyperfractionated radiotherapy. There was no significant difference in the two-year incidence of brain metastases between the standard-dose group and the higher-dose group, 29% and 23%, respectively (HR 0.80, 95% CI 0.57–1.11; $p = 0.18$). Moreover, mortality was increased in the high-dose group, with two-year OS of 42% and 37% respectively (HR 1.20, 95% CI 1.00–1.44; $p = 0.05$). The excess in mortality remains unexplained, as there was no excess of treatment-related deaths in this group. Long-term follow up revealed no significant difference between the two groups in any of the 17 selected items assessing quality of life, neurological, and cognitive functions. In both groups a mild deterioration across time of communication deficit, weakness of legs, intellectual deficit, and memory was observed (all $p < 0.005$). [40] The standard dose of PCI (25 Gy in 10 fractions) therefore remains the standard of care in stage I–III SCLC patients.

4. Conclusion

With the development of personalized medicine, there has never been a better time for the LCG to break down country barriers and develop research strategies to answer difficult clinical questions while studying the biology of lung cancer in all its forms. This is the challenge, and with support from colleagues in other EORTC Groups and the staff at EORTC Headquarters, we can respond to this challenge.

5. Conflict of interest statement

Corinne Faivre Finn and Veerle F. Surmont declare no conflicts of interest. Jan P. van Meerbeeck consulted for AstraZeneca, received honoraria from GSK, received honoraria and research funds from Hospira, and received travel reimbursement from Boehringer Ingelheim and MSD. Mary E.R. O'Brien consulted for and received research funds from Pierre Fabre, consulted for and received research funds and travel reimbursement from Roche, consulted for and received travel reimbursement from Hospira, received research funds and travel reimbursement from Boeringer, received travel reimbursement from Lilly, and received research funds from GSK.

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