LUNG CANCER

David Ball
Lung Service, Peter MacCallum Cancer Centre, East Melbourne, Victoria.
Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Victoria
Email: david.ball@petermac.org

Abstract

Almost untreatable in 1973, except by surgery, lung cancer is now susceptible to radiotherapy and chemotherapy as well, and is often treated by all three modalities in combination. Although tobacco is the major cause of lung cancer, specific subtypes of the disease due to mutations unrelated to smoking have been recently identified, and have opened up opportunities for 'personalised' therapy. While these developments in treatment have led to a reduction in lung cancer mortality, by far the biggest factor contributing to the declining death rate has been the success of public health campaigns directed at reducing tobacco consumption.

In 1973, the Australian lung cancer epidemic was at its peak, yet the only treatments available were surgery for the small proportion of patients with operable early stage cancers, and palliative radiotherapy for more advanced cases. An influential but nihilistic British trial had shown that active treatment was no better than best supportive care.[1] The message was clear: only prevention through reduced tobacco consumption could reduce the number of deaths. As a result of this trial, progress in the treatment of non-small cell lung cancer (NSCLC), in particular, stalled and it would be another two decades before evidence became available that treatment could alter the natural history of inoperable NSCLC. Since 1973, the character of the disease has changed. Squamous cell cancer was replaced by adenocarcinoma as the most common form of NSCLC, and the proportion of small cell lung cancer (SCLC) fell to 15% of all lung cancers. Lung cancer mortality has fallen, partly a result of more effective treatment, but mostly the consequence of successful public health policy in which Australian campaigners have a proud and internationally acclaimed record. Strategies championed by the health lobby which have resulted in reduced tobacco consumption have included media advertising, using confronting images, and punitive taxation.[2]

This review will however, now focus on practice changing treatment developments decade by decade; citations which were either Australian or had a significant Australian contribution are underlined.

1970s: understanding and mapping the disease

The importance of stage (disease extent) and performance status as critical prognostic factors came to be recognised in studies by the Veterans Administration Lung Cancer Group in the US.[3] One of the most important developments in this decade was the introduction of computed tomography of the chest for disease staging and radiotherapy planning.[4] The distinct nature of small cell lung cancer, with its more aggressive natural history and propensity for early distant metastasis, came to be appreciated, with a resulting shift away from surgical resection to systemic therapy. Initially, this consisted of single agent alkylating agents,[5] and then combination chemotherapy.[6] It was also at this time that a possible role for prophylactic cranial irradiation was suggested by Hansen, although it would be 15 years before an impact on survival could be demonstrated.[7,8]

1980s: the small cell cancer decade

In the landmark RTOG 7301 trial, 60 Gy was established as the most effective radiotherapy dose for locally advanced NSCLC and it has remained the standard of care to now.[9] But the 1980s really belonged to SCLC. Non-platinum containing regimens gave way to combinations containing cisplatin, and then carboplatin.[10,11] It was also in this decade that the addition of thoracic radiotherapy to chemotherapy in patients with limited disease was shown to improve survival,[12-13] later confirmed by meta-analysis.[14]

1990s: treatment for NSCLC works as well

Although the activity of platinum based agents had been demonstrated in NSCLC during the 1980s,[15] the effect on survival and quality of life remained contentious.[16] Then, after two decades of negligible progress, the combination of cisplatin and radiotherapy administered either sequentially,[17] or concomitantly,[18] was shown to improve survival compared with radiotherapy alone in patients with inoperable NSCLC. For the most common scenario – metastatic disease – the landscape changed in 1995 when a practice-changing meta-analysis confirmed that cisplatin chemotherapy did indeed increase survival compared with best supportive care in advanced NSCLC,[19] and so the modern era of NSCLC treatment began.

In surgery, lobectomy was shown to be superior to limited resection for stage I NSCLC,[20] and the first references to the use of video-assisted thoracic surgery began to appear.[21] In radiotherapy, shortening the overall treatment time with multiple treatments per day produced a survival benefit in both NSCLC,[22] and SCLC,[23] subsequently confirmed in meta analysis.[24]

In imaging, the first reports of the impact of fluorodeoxyglucose (FDG) PET scanning – which would revolutionise the staging and management of NSCLC in the next decade – were published.[25-26]

2000 onwards: the desert blooms.

Chemotherapy was by now an established standard

of care for good performance status patients with metastatic NSCLC, and various platinum-based regimens containing two drugs seemed to be similarly effective.[27] If chemotherapy prolonged survival in patients with advanced disease, might it not be even more effective in patients with subclinical metastatic disease, as was the case in patients with breast cancer? The IALT study of adjuvant platinum based chemotherapy in patients with completely resected early stage NSCLC was the first to confirm that adjuvant chemotherapy did improve survival.[28] This was confirmed by a subsequent meta analysis.[29] In patients with unresectable locally advanced NSCLC, concomitant chemotherapy and radiotherapy were shown to be superior to sequential treatment.[30]

Recognition that there are lung cancers arising in non-smokers which are associated with specific mutations - some of which occur with greater frequency in particular ethnic populations – dramatically changed the perception that lung cancer was only a disease of smokers. The demonstration that tyrosine kinase inhibitors could prolong progression free survival in patients with EGFR mutations,[31] and that crizotinib was active against tumours with ALK gene rearrangements,[32] opened up a new range of treatment options, and the era of personalised targeted therapies was born, with treatment based on molecular profiling rather than light microscopy.

In other developments, a new non-surgical treatment option for patients with stage I NSCLC appeared in the form of hypofractionated stereotactic radiotherapy,[33] and its role is undergoing refinement. The TNM staging system was revised in 2009, based on over 100,000 cases, the result of a huge international collaboration.[34] Finally, the ability to detect early stage lung cancer by CT screening and so reduce mortality was confirmed by a large randomised trial.[35]

Conclusion

In 2013, survival for lung cancer remains among the worst for any cancer, but as the last four decades have demonstrated, the research effort has accelerated with demonstrable improvements in outcomes. While progress in SCLC treatment has slowed, there is no sign of that in NSCLC, and the challenge now is to identify the most promising of the many strategies available for further research.

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HAEMATOLOGICAL MALIGNANCIES - INTRACTABLE OBSTACLES AND PATH FINDING BREAKTHROUGHS OVER 40 YEARS

James F Bishop
Victorian Comprehensive Cancer Centre, Melbourne, Victoria.
Herman Chair of Cancer Medicine, University of Melbourne, Melbourne, Victoria.
Email: jim.bishop@unimelb.edu.au

Abstract

Haematological malignancies have identified the path forward for oncology, initially with systemic treatment and combination chemotherapy and limiting the need for or extent of radiotherapy. In recent years, important targeted therapies were first demonstrated as practical with the first tyrosine kinase inhibitors, the first monoclonal antibodies and the extensive genetic characterisation and classification of these diseases. The genomic era holds the promise of further, more rapid progress, with remaining intractable problems such as poor outcomes overall with acute myeloid leukaemia, both primary and secondary, and possibly new therapy that could avoid the short and long-term side-effects of curative chemotherapy. The extensive sub-classification of leukaemia and lymphoma into smaller sub-sets have made some large scale clinical trials a challenge and may have flagged an emerging obstacle to progress in cancer trials more generally.

During the past four decades, significant progress has been made in identifying the molecular pathogenesis of lymphomas as a clonal expansion of B cells, in the majority, and of T cells. Similarly, our understanding of leukaemia has increased dramatically with the identification of the genetic abnormalities fundamental to the disease process. Such knowledge has led to major breakthroughs in the classification and treatment of these diseases.

Chemotherapy in the beginning

While Paul Ehrlich first coined the phrase 'chemotherapy', modern systemic therapy was ushered in by the serendipitous observation that accidental exposure to mustard gas caused bone marrow failure. The resulting application of alkylating agents and combination chemotherapy to leukaemia and lymphoma in clinical trials had early success, leading to the promise of cures in these diseases and decades of progress in cancer.

In reality, there has been good progress in lymphoma and childhood leukaemia, but many other cancers have quickly surpassed gains in acute myeloid leukaemia (AML) in the modern era. In Australia, five year survival from AML was around 10% in the late 1980s, and remains only 24% currently, although some sub-sets do better.[1] In contrast, Hodgkin's disease has a five year survival of 88%, non-Hodgkin's lymphoma (NHL) 71% and all cancer 66%.

Standard induction therapy for AML remains based on anthacycline and cytarabine, with seminal trials of high dose cytarabine induction conducted in Australia.[2] Major advances in AML have included understanding of the importance of genetic changes for classification and prognosis, use of all-trans-retinoic acid in acute promyelocytic leukaemia,[3] and haematopoietic stem cell transplantation. Targets for future advances could include mutations in FLT3, RAS and other genetic mutations affecting cellular pathways that confer a proliferative or survival advantage for leukaemia cells. Another set of mutations associated with improved differentiation and self renewal could be subject to all-trans-retinoic acid or histone deacetylase or other inhibitors. Haematopoietic stem cell transplantation offers the possibility of cure to individuals, especially in first complete remission. Use of risk stratification based on initial genetic profile and subsequent post-induction bone marrow examinations has been an important area of progress in haematopoietic stem cell