From Poison to Precision: One Patient with Lung Adenocarcinoma Across Oncology Eras

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Abstract

Advanced lung adenocarcinoma has historically been associated with poor survival and substantial treatment-related morbidity, reflecting limited diagnostic precision and non-selective therapeutic strategies. This case-based review traces the evolution of management through three eras using a representative presentation of a 60-year-old woman with advanced disease. In the 1970s–1980s, diagnosis relied on chest radiography, sputum cytology, and invasive biopsy, with inaccurate staging due to limited imaging and no molecular characterization. Treatment was largely palliative, centered on radiotherapy, surgery in select cases, and first- and second-generation platinum-based chemotherapy, which offered modest survival benefits at the cost of significant toxicity. Contemporary management in the 2020s is defined by next-generation sequencing and molecular stratification, enabling the identification of actionable oncogenic drivers and immune biomarkers. Tyrosine kinase inhibitors targeting EGFR, ALK, and other alterations, alongside immune checkpoint inhibitors directed at the PD-1/PD-L1 axis, have transformed outcomes, delivering improved survival, reduced severe adverse events, and durable disease control in selected patients. Looking ahead, emerging innovations promise further individualization of care. Personalized neoantigen vaccines derived from tumour-specific sequencing aim to elicit highly targeted immune responses with minimal off-target toxicity, particularly when combined with immune checkpoint blockade. Collectively, these advances illustrate a paradigm shift from broadly cytotoxic therapy toward precision oncology, highlighting both the rapid progress achieved in lung adenocarcinoma management and the substantial opportunity to further improve patient outcomes in the decades ahead.

Introduction

The treatment of lung adenocarcinoma has undergone a profound transformation over the past century, evolving from broadly cytotoxic chemotherapy toward increasingly personalised and molecularly targeted therapies. To illustrate this evolution in oncological treatment, this paper follows the management of a single hypothetical patient across successive eras of care. A 60-year-old woman with a history of smoking presents to the emergency department with a six-month history of progressively worsening cough associated with haemoptysis, chest pain, dyspnoea, and unintentional 15 kg weight loss.

Clinical assessment is highly suggestive of advanced lung adenocarcinoma.

In the early and mid 20th century, management options were limited, with first-generation and later platinum-based chemotherapy forming the cornerstone of treatment (1,2). Although these cytotoxic approaches conferred modest survival benefits, they were associated with substantial toxicity and poor quality-of-life outcomes. Advances in diagnostic evaluation and an improved understanding of tumour immunobiology led to the introduction of immunotherapeutic strategies, many of which remain central to current practice (3).

These approaches improved survival and tolerability compared with traditional chemotherapy, yet still lacked precise specificity for the molecular drivers of tumour growth. Emerging frontiers in lung cancer treatment seek to address this limitation through comprehensive tumour sequencing, personalized neoantigen identification and therapeutic cancer vaccines (4). Consequently, the therapeutic approach and anticipated outcomes for this patient differ markedly depending on the era in which she presents, underscoring the dramatic evolution of lung adenocarcinoma management from broadly cytotoxic therapy toward precision oncology.

Historical Management: The Cytotoxic Era

A patient with advanced lung adenocarcinoma would likely experience significant challenges with receiving treatment before the 1980s. In the 1970s, this patient would have relied mainly on chest X-rays, sputum cytology, and bronchoscopy with biopsy for diagnosis and staging. Although CT scans were introduced in the 1970s, their clinical feasibility was limited, and evidence supporting their use to improve early detection emerged in the next decade (5). While histological subtyping was possible, molecular characterization was unavailable, and adenocarcinoma was not recognised as a biologically distinct entity. The absence of PET imaging and advanced MRI further contributed to inaccurate staging, meaning diagnosis and treatment frequently occurred only after symptom onset (5).

Early chemotherapy regimens evaluated nitrogen mustard in bronchogenic carcinoma in the 1940s, followed by the use of alkylating agents in the 1960s (1,2). These single-agent therapies yielded modest benefits, improving overall survival by only 2–4 months (1). In the 70s, these single agents were used in combined therapeutic regimens referred to as CAMP (Cyclophosphamide, Adriamycin, Methotrexate, and Procarbazine) or MACC (Methotrexate, Doxorubicin, Cyclophosphamide, and Lomustine) in attempts to increase drug efficacy (2). A more meaningful therapeutic advance occurred with the introduction of second-generation platinum-based agents in the 1980s and 1990s.

Cisplatin and carboplatin demonstrated superior efficacy over non-platinum regimens, increasing median overall survival to 5–7 months, with objective response rates of 20–30% and one-year survival of 10–20% (1,2). Combination regimens pairing cisplatin with plant alkaloids or podophyllotoxins, particularly etoposide, produced the most favourable outcomes, with one-year survival rates reaching 25% (1,2,6). Despite these improvements, platinum agents acted indiscriminately on rapidly dividing cells, enabling their use across multiple tumour types regardless of histology, but at the cost of significant toxicities including gastrointestinal toxicity, nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression (1,6). Chemotherapy dosing was individualized, with guidelines recommending four to six cycles administered every three to four weeks, tailored to haematological and renal function, particularly for cisplatin given its extensive renal excretion (1,6).

Surgery also emerged as a cornerstone of early-stage NSCLC management during the 20th century, though advanced tumours frequently precluded resection. Open thoracotomy with lobectomy was standard, while pneumonectomy was reserved for extensive disease, with high rates of incomplete resection and local recurrence (7). Radiotherapy was widely used in the 1970s, particularly for inoperable stage III disease, with two-dimensional planning and standard dosing of 60 Gy over six weeks contributing to treatment-related toxicity (8,9). Improvements in CT imaging in the 1980s enhanced radiotherapy precision, allowing its role to evolve from primarily palliative to an adjunct to surgery and chemotherapy, with associated survival gains (9). Supportive care during this era remained focused on symptom relief, with limited integration of structured palliative services (10). Overall, for a 60-year-old woman presenting with advanced lung adenocarcinoma during this period, treatment options were constrained, largely palliative, and associated with poor survival outcomes.

Contemporary Management: The Precision and Immunotherapy Era

In the 2020s, next-generation sequencing (NGS) has become central to the diagnostic evaluation of advanced lung adenocarcinoma, enabling molecular stratification into tumours with actionable driver mutations and those without (3). For this 60-year-old woman presenting with advanced disease today, this molecular stratification would occur at diagnosis and would immediately guide first-line treatment selection, in contrast to historical approaches that relied solely on tumour histology.

Within this framework, immune checkpoint inhibition targeting the programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) pathway has emerged as a cornerstone of management for EGFR wild-type adenocarcinoma. In this patient population, tumours are typically more immunogenic and rely on PD-1/PD-L1–mediated immune evasion rather than oncogene-driven signalling; blockade of this pathway restores effective antitumour T-cell responses (11). In EGFR wild-type metastatic lung adenocarcinoma, PD-L1 testing would guide therapy for this woman. If her tumour demonstrated high PD-L1 expression (tumour proportion score $\geqslant$50%), pembrolizumab monotherapy would be established as standard care following the KEYNOTE-024 trial, which demonstrated superior overall and progression-free survival compared with platinum-based chemotherapy, alongside fewer high-grade treatment-related adverse events, thereby offering her both prolonged survival and improved tolerability (12). If her tumour had lower or absent PD-L1 expression, combination platinum–pemetrexed chemotherapy with pembrolizumab would be recommended after KEYNOTE-189 showed a significant overall survival benefit over chemotherapy alone, extending survival beyond what was achievable in earlier eras (13).

Alternatively, if this woman's tumour harboured an activating EGFR mutation, her prognosis would be fundamentally altered through targeted tyrosine kinase inhibition.

First-generation EGFR TKIs, including gefitinib and erlotinib, demonstrated clear superiority over platinum chemotherapy in IPASS and EURTAC, with higher response rates, longer progression-free survival, and improved quality of life (14). These gains were further enhanced with the third-generation TKI osimertinib, which established a new standard of care after the FLAURA trial demonstrated superior progression-free and overall survival, improved central nervous system control, and better tolerability compared with earlier TKIs, allowing patients such as this woman to achieve sustained disease control (15). Comparable advances have occurred in other oncogene-driven subsets; for example, in ALK-rearranged disease, alectinib significantly prolonged progression-free survival and reduced CNS progression compared with crizotinib (16). Importantly, recognition that EGFR-mutant tumours respond poorly to PD-1/PD-L1 blockade has refined treatment sequencing for patients like this woman, avoiding ineffective therapy and unnecessary toxicity (17).

Collectively, these precision-based strategies have shifted the prognosis for women like this patient from median survival measured in months to the realistic possibility of multi-year disease control with preserved quality of life, marking a significant departure from the outcomes associated with historical cytotoxic regimens (12,13,18).

Future Management: The Personalized and Adaptive Precision Oncology Era

The future of non-small cell lung cancer (NSCLC) treatment is moving toward fully personalized precision oncology, using comprehensive tumour sequencing to identify unique neoantigens and enable individualized immunotherapies. For a patient such as the 60-year-old woman described in this case, high-throughput sequencing would allow detailed characterization of her tumour's molecular profile, facilitating the selection of patient-specific neoantigens (19–22).These neoantigens can be incorporated into personalized cancer vaccines delivered via peptide, mRNA, or dendritic cell platforms, priming her immune system to recognize and eradicate tumour cells while minimizing off-target effects (4).

Early-phase clinical trials in NSCLC have demonstrated that personalized neoantigen vaccines, particularly when combined with immune checkpoint inhibitors, elicit robust T-cell responses and show promising safety and immunogenicity profiles, with evidence of epitope spreading and increased tumour infiltration by effector T cells (19,22,23). Cancer vaccines have also been shown to prolong survival in patients with advanced NSCLC following first-line therapy (24), suggesting the potential for improved long-term disease control for patients like this woman. Ongoing studies are exploring the integration of these vaccines with standard therapies to overcome resistance and further improve outcomes.

Alongside advances in immunotherapy, Artificial intelligence (AI) is increasingly being incorporated into the management of NSCLC, particularly in imaging analysis, molecular profiling, and prediction of treatment response. AI-assisted radiologic interpretation has shown potential in improving early detection and characterization of pulmonary nodules (25), while machine learning models may help identify patients most likely to benefit from targeted therapies or immunotherapy(26). As precision oncology continues to evolve, AI may further support individualized treatment strategies in NSCLC care.

Should this patient present in the future, emerging advances such as personalized neoantigen vaccines and AI-supported precision oncology may further expand treatment options for advanced NSCLC. These developing technologies reflect the ongoing shift toward increasingly individualized cancer care, with the potential to improve therapeutic selection and long-term disease management.

Conclusion

Examining the evolution of lung adenocarcinoma treatment across multiple decades highlights the profound advances achieved within the field of oncology. In the 1970s and 1980s, a 60-year-old woman presenting with advanced lung disease would have faced care limited by imprecise diagnostics, late-stage presentation, and largely non-selective therapies that offered only modest benefit at the cost of significant toxicity. In contrast, contemporary management is shaped by molecular profiling and immunologic characterization, enabling a far more targeted and personalized therapeutic approach. Innovations such as next-generation sequencing and immune checkpoint inhibition have greatly improved survival outcomes and quality of life in patients with advanced lung adenocarcinoma. Emerging developments including personalized neoantigen vaccines and AI-driven precision oncology models further reflect the ongoing shift toward increasingly individualized cancer care. Together, these advances mark a transition from broadly cytotoxic treatment toward precision oncology. This paper underscores the substantial evolution of lung cancer management over multiple decades and highlights the significant potential that remains to further improve outcomes for patients diagnosed in the future.

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