Editorial

Adaptive medicine, a crucial component of optimized decision making: perspectives from lung cancer management

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The concept of adaptive treatment, originally rooted in the domain of radiation treatment, serves as a testament to the nuanced approach required in tailoring treatment dosages to the distinct variances observed in lung cancer patients (1). Recently, increasing discussions have been made on the pivotal role of adaptive treatment in lung cancer, which advocates for judicious alterations to establish treatment protocols tailored to the unique therapeutic scenario (2). We herein advance the idea of expanding adaptive treatment into a broader framework of adaptive medicine for the integrated management of lung cancer, covering all facets from prevention and screening to diagnosis and treatment. This study underscores adaptive medicine as a crucial component of optimized decision-making, providing unique perspectives for the management of lung cancer.

Adaptive medicine has emerged in response to the substantial heterogeneity of lung cancer, which is manifested not only among tumors from different patients but also within the tumor. Traditional therapeutic approaches often fall short in addressing this diversity, which encompasses variations from genetic mutations to epigenetic modifications and phenotypic differences. Evidence-based medicine advocates for the establishment of standardized treatment protocols based on large population studies, such as categorizing lung cancer patients according to the tumor-node-metastasis (TNM) staging system and implementing corresponding treatments. With technological advancements enabling more detailed patient stratification, medical decisions can be optimized by considering each patient's genetic information, disease characteristics, personal health history, and other factors. In this context, precision medicine and adaptive medicine have garnered significant attention.

In the field of lung cancer, within the framework of established guidelines that offer standardized, evidence-based medical advice to broad populations, precision medicine stands out by classifying individuals based on their unique pathological or genetic markers, which customizes therapeutic strategies specifically tailored to such classifications. Adaptive medicine employs a variety of tools to stratify populations by risk, allowing for the dynamic adjustment of medical decisions based on individual needs. Personalized medicine takes a comprehensive approach by incorporating a wide range of patient-specific characteristics and preferences into the development of individualized medical plans. Driven by rapid technological progress, these innovative approaches are transforming the medical field, ensuring that treatment strategies are closely aligned with the distinct biological and personal attributes of each patient. This transformation signifies a fundamental shift from traditional, one-size-fits-all medical care to a more refined, patient-focused medical decision (*Figure 1*).

There are several critical pathways in implementing

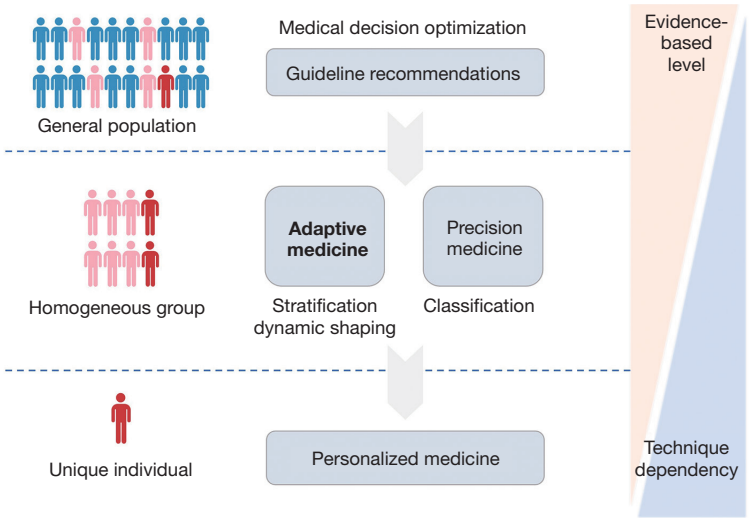

Figure 1 Strategy evolution for medical decision optimization in lung cancer.

adaptive medicine. Firstly, the application of clinical features involves integrating and utilizing a wealth of clinical, radiological, and molecular data based on patient characteristics. This includes adjusting clinical models, such as using big data for further lung cancer classification and predicting prognosis or treatment response (3,4). Secondly, strategic optimization involves the inclusion of subtractive strategies, such as reducing chemotherapy, as well as additive strategies, which encompass the integration of local treatments and strategic modifications. These modifications can include concurrent and sequential chemoradiation, rotation of targeted therapies, and adjustments in treatment methods such as timing and cycles, etc. All these measures fall within the scope of strategic optimization in treatment. Thirdly, monitoring molecular biomarkers, notably the implementation of minimal residual disease (MRD) based on circulating tumor DNA (ctDNA) and other molecular markers such as tumor markers, tumor mutational burden (TMB), programmed death-ligand 1 (PD-L1), tumor microenvironment (TME)-related immune cells, tumor neoantigen burden (TNB), and more, awaits further researches to clarify their roles in guiding medical decisions (5).

The successful implementation of adaptive medicine crucially hinges on the precise integration of clinical features, strategic optimization, and rigorous monitoring of molecular biomarkers, with artificial intelligence (AI) playing a pivotal role. AI-based technologies significantly strengthen real-time clinical decision-making, thereby advancing personalized medicine (6). It is particularly important to highlight that lung cancer patients' clinical manifestations and molecular characteristics may change. Thus, real-time dynamic adjustments are emphasized in the practice of adaptive medicine.

Adaptive strategy plays a crucial role in managing early-stage non-small cell lung cancer (NSCLC). For instance, our study provided a non-risk-based strategy for low-dose computed tomography screening, offering evidence for expanding the screening population beyond current guidelines (7). Utilization of AI technologies to integrate high-throughput, targeted DNA methylation sequencing of ctDNA with imaging results aids in distinguishing between benign and malignant pulmonary nodules. Additionally, AI technology aids in predicting specific genetic mutation types through imaging techniques, thereby improving the diagnosis of early-stage lung cancer (8-10). These tools demonstrate the feasibility of non-invasively detecting early malignancies, thereby reducing the occurrence of unnecessary or delayed surgeries.

Treatment for early-stage lung cancer primarily involves surgery and postoperative adjuvant therapy. The concept of tubeless video-assisted thoracoscopic surgery (VATS) avoids intraoperative intubation, post-operative chest tube placement, and urinary catheterization, offering a minimally invasive procedure for patients with suspected malignant lung nodules (11). Determining the necessity for adjuvant therapy after lung surgery depends on assessing the patient's risk of recurrence. ctDNA MRD has emerged as a potential biomarker for the prediction of recurrence in lung cancer.

Another predictive model for postoperative lung cancer recurrence leverages RNA expression profiles from surgical specimens. Using a 14-gene prognostic assay can identify specific stage IA patients who may benefit from epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) (12). The necessity of adjuvant chemotherapy comes into question when targeted therapies show promising results (13). We observed no benefit of chemotherapy in postoperative NSCLC patients who received osimertinib according to the cross-arm comparison of the ADAURA study. By adopting a subtractive treatment strategy, adjuvant chemotherapy may not be essential for patients with EGFR-mutant NSCLC (14).

The advancement in the management of locally advanced NSCLC underscores the promise of adaptive medicine, as seen in multifaceted treatments like the combination of radiotherapy and immunotherapy. As an alternative solution, one of our studies suggests that for patients initially deemed unresectable with stage IIIB lung cancer, surgical resection becomes feasible after a combination of immunotherapy and chemotherapy (15). A recent meta-analysis suggests that adding programmed cell death 1 (PD-1) or PD-L1 inhibitors in the adjuvant phase to neoadjuvant treatment with PD-1 or PD-L1 inhibitors and chemotherapy may not improve survival outcomes for patients with resectable NSCLC and may be associated with increased adverse events (16).

In advanced NSCLC, adaptive medicine holds particular importance, especially for patients with oligoprogressive or oligometastatic disease. Additive treatments for oligometastatic patients should be selective, such as determining optimal candidates for primary tumor resection based on population modeling. By classifying stage IV NSCLC patients from the Surveillance, Epidemiology, and End Results (SEER) database and conducting 1:1 propensity score matching, we analyzed median cancer-specific survival (CSS) times between the surgery and non-surgery groups; a practical predictive model was created and might be used to identify the optimal candidates for surgical resection of the primary tumor among stage IV NSCLC patients who were regarded as inoperable (17).

When combined with dynamic monitoring, comprehensive treatment approaches, including targeted therapy, immunotherapy, chemotherapy, and others, can optimize treatment outcomes. For example, the detection of EGFR mutations in ctDNA is an effective method to identify patients who might benefit from EGFR-TKIs. In the BENEFIT study, the clearance rate of EGFR mutations at 8 weeks in plasma could predict early resistance to gefitinib, indicating the importance of dynamic genetic testing in managing disease progression. Further analyses of dynamic alterations of EGFR mutations and accompanying gene aberrances could predict resistance to gefitinib. The analysis identified three patient subgroups based on baseline NGS data: those with only EGFR mutations, those with mutations in both EGFR and tumor-suppressor genes, and those with mutations in both EGFR and oncogenes, with median progression-free survival (PFS) of 13.2, 9.3, and 4.7 months, respectively (18). The FOCUS-C study explores the efficacy of using ctDNA to guide therapy in patients with advanced EGFR mutant NSCLC and investigates whether monitoring the clearance of EGFR ctDNA from blood can inform the choice between furmonertinib monotherapy or its combination with chemotherapy and/or bevacizumab to improve patient outcomes. Those with persistent EGFR ctDNA after initial treatment are then randomized to receive further treatment combinations. The results of this ongoing study are anticipated for further guidance in clinical practice (19). Local consolidative therapy (LCT) has been established to enhance the overall survival rates of patients with advanced NSCLC undergoing targeted therapy, leading to recommendations for the continued use of such therapies. Nevertheless, the potential benefits of a pause in targeted therapy—referred to as a drug holiday—for patients who have no visible lesions and have achieved negative MRD status after LCT remain unclear. A recent study suggested that a drug holiday based on MRD status was feasible for patients treated with EGFR-TKI based on LCT (20). The above studies suggest that patients with EGFR-sensitive mutations require a more refined management.

In the era of immunotherapy, the substantial efficacy of immunotherapy prompts an inquiry into the necessity of integrating chemotherapy. We comprehensively compared the therapeutic efficacy and safety of PD-1/L1 antibodies, chemotherapy, and their combination as primary treatments for advanced NSCLC. In an indirect comparison, the combination of PD-1/L1 antibodies and chemotherapy proved superior in terms of PFS compared to PD-1/L1 antibodies alone, even for patients with high PD-L1 expression (≥50%). Thus, we suggest that a combination regimen is preferable as a first-line treatment for NSCLC patients with different PD-L1 expressions while being cautious of side effects (21).

Nevertheless, in combined immunotherapy and chemotherapy regimens, the necessity for sustained

administration of chemotherapy remains a heated debate. We explored chemo-free regimens, with immunochemotherapy being the standard first-line treatment for NSCLC. This study aims to compare the clinical efficacy of different first-line maintenance regimens for advanced EGFR/ALK-negative NSCLC and explore the eligibility of chemo-free maintenance. Our findings show that following first-line immunochemotherapy, chemo-free maintenance by immune checkpoint inhibitors (ICIs) plus anti-angiogenesis and on-demand chemo-rechallenge provided comparable PFS outcomes to chemo-on maintenance, thus minimizing cytotoxic drugs without compromising therapeutic effectiveness (22).

Incorporating adaptive medicine into lung cancer management represents a paradigm shift towards personalized, precision-driven care. In lung cancer populations, managing concurrent diseases like chronic obstructive pulmonary disease (COPD) alongside lung cancer demands careful consideration (23,24). Adaptive medicine emphasizes the necessity of real-time assessment of patients' conditions. For example, the recommendation to postpone adjuvant chemotherapy during the coronavirus disease 2019 (COVID-19) pandemic illustrates this adaptability (25). In summary, adaptive medicine provides a multidimensional framework for continuously refining and optimizing decision-making to meet the needs of individual patients and adjust according to the dynamic trajectory of disease progression. With ongoing research and emerging new technologies, adaptive medicine is expected to play a central role in managing lung cancer patients.

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