

EDITORIAL

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Immunotherapy of Lung Cancer in Countries with Limited Resources; Current Challenges and Potential Solutions

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Lung cancer stands out as the most commonly diagnosed form of cancer and the leading cause of cancer-related mortality on a global scale [1]. GLOBOCAN 2020 data shows that lung cancer was the leading cause of cancer death and new cases among men in Iran in 2020. The study also estimated that globally, there were roughly 2.2 million new lung cancer cases (11.4%) and 1.8 million lung cancer deaths (18.0%) that year [1].

In Iran, lung cancer (LC) is diagnosed less frequently compared to western countries [2]. A previous study indicated the ASIR for lung cancer has increased from 1.3 (0.7–1.9) in 1990 to 8.9 (7.3–10.5) in 2016 [3]. However, the study found that the death rate from lung cancer remained fairly consistent over the 27 years studied [3]. Squamous cell carcinoma (SCC) was the most common type of lung cancer in Iranian men, while adenocarcinoma (AC) was most frequent in Iranian women. Additionally, a very high percentage (85.3%) of the patients had advanced stages of the disease.

Immune checkpoint inhibitors have shown tremendous benefits in the treatment of non-small cell lung cancer (NSCLC) and are now being used as first-line therapies in metastatic disease, consolidation therapy following chemoradiation in unresectable locally advanced disease, and adjuvant therapy following surgical resection and chemotherapy in resectable disease [4]. Immunotherapy is revolutionizing the landscape of cancer treatment due to its demonstrably favorable safety profile, the induction of long-lasting therapeutic benefit through the establishment of immunological memory, and its broad applicability across diverse patient populations especially when it comes to patients with lung cancer who are diagnosed mostly in elderly and patients are mostly fragile [4]. Targeting immune checkpoint molecules, particularly cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) axis, has emerged as the most efficacious immunotherapeutic approach in NSCLC. CTLA-4 blockade promotes enhanced intratumoral infiltration and diversification of tumor-

specific T lymphocytes, while PD-L1/PD-1 checkpoint inhibitors function by abrogating the suppression of T cell effector activity [4]. The preliminary data on effectiveness of immunotherapy in NSCLC comes from CheckMate-012 in 2016 when investigators showed that nivolumab can induce durable responses with appropriate safety profile when prescribed as a monotherapy in IIIB to IV NSCLC patients [5]. Simultaneously, KEYNOTE-024, a phase 3 trial, showed that stage IV NSCLC patients benefit significantly from pembrolizumab, a PD-L1 inhibitor comparing to chemotherapy [6]. However, the utility of immunotherapy is not limited to the metastatic setting and locally advanced diseases. IMpower010 has provided the first evidence that atezolizumab, a PD-L1 inhibitor, improves the survival rates of nonmetastatic NSCLC patients (stages IB-III A) when prescribed as a maintenance treatment following surgery and adjuvant chemotherapy [7]. Subsequently, KEYNOTE-091 trial provided further evidence in support of maintenance pembrolizumab in early-stage NSCLC [8].

Efficacy of immunotherapy basically depends on PD-L1 tumor proportion score and Tumor Mutational Burden (TMB) [9]. The delivery of comprehensive oncological care presents a significant challenge within developing countries. This disparity is further amplified when considering the stark contrast in access to, and quality of, cancer treatment between high-income countries (HICs) and low- and middle-income countries (LMICs) [10]. The equitable access to, and utilization of, novel immunotherapies in developing countries remains significantly hindered by both availability constraints and substantial cost burdens [11]. In Iran, Furthermore, in geographically disparate regions with lower population density, the availability of general oncologists falls demonstrably short of the requisite number to meet the oncological needs of the population. This disparity is even more pronounced for sub-specialists in the field of immuno-oncology [12]. To deal with the new immune-related side effects, there is a need to train and employ specialists in immuno-oncology which will

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extend the cost of the use of these two immunotherapies far beyond their initial price tags [11,12]. Recently, some investigations identified modifiable factors at the provider, organizational, and societal levels as posing significant impediments to the effective implementation of community-based policies [13]. These factors, therefore, present crucial targets for intervention aimed at improving policy outcomes [12].

Bridging the gap in healthcare requires a deeper exploration of the underlying reasons for these inequalities [12]. Conceptually, the ability to effectively address an issue grows as we move from individual actions to interventions by providers, organizations, and finally, social policies. This happens because there are fewer things to address at each level, but the impact of those changes becomes broader [12]. In Iran, the high economic burden associated with original immunotherapy and biosimilar medications has been mitigated by the development and production of domestic alternatives. This has demonstrably improved patient access to these life-saving treatments. However, The need for designing a comprehensive guideline for providing immune oncology care based on different access level in health care system is essential in the country. Also, prioritizing new treatment protocols considering modified dose response recommendations available for low- and middle-income countries [14] could help wider access to immune oncology drugs.

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