Lung cancer is the leading cause of cancer-related death in the world. Non-small cell lung cancer (NSCLC), accounting for approximately 80% to 85% of all lung cancers, is a heterogeneous combination of various histologies that include squamous cell carcinoma, adenocarcinoma and large cell carcinoma. The majority of patients with NSCLC will have advanced-stage, non-operable disease at the time of diagnosis. The goal of treatment in advanced NSCLC is to slow down the progression of the disease, improve symptoms and overall survival (OS). The standard treatment of advanced NSCLC has been systemic chemotherapy. In 1995, a meta-analysis showed that cisplatin based chemotherapy resulted in a 27% reduction in the risk of death and a 10% improvement in survival at 1 year. Accurate histologic differentiation of NSCLC (squamous carcinoma Vs non-squamous histology) is important in the selection of chemotherapy agents. A randomized trial of cisplatin plus gemcitabine Vs. cisplatin plus pemetrexed in patients with advanced NSCLC reported that non-squamous patients had a longer median survival on cisplatin/pemetrexed (11 months) than on cisplatin/gemcitabine whereas squamous patients had a median survival of 10.8 months on cisplatin/gemcitabine compared to 9.8 with cisplatin/pemetrexed. Although most patients will progress after receiving first-line chemotherapy, there are currently several chemotherapeutic agents (docetaxel, pemetrexed and erlotinib) available in the second-line setting.

While newer chemotherapy agents resulted in improved outcomes in survival in advanced NSCLC, a therapeutic plateau was reached, with a median overall survival of approximately 8-10 months and no single regimen demonstrating significant superiority over any other combination. A better understanding of cancer biology led to the identification of several potential molecular targets for cancer treatment such as vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) and epidermal growth factor receptor (EGFR) resulting in major progress in the therapeutic landscape of NSCLC. In a phase II trial comparing chemotherapy plus the VEGF monoclonal antibody bevacizumab (BCP) versus chemotherapy alone (CP) revealed that life-threatening or fatal hemoptysis occurred in 4 of 13 patients with squamous cell histology who received the BCP and thus bevacizumab has been restricted to non-squamous histology. In a randomized trial in patients with advanced non-squamous NSCLC, BCP resulted in significantly longer OS compared to chemotherapy alone (12.3 vs 10.3 months, respectively; HR 0.80, \( P=0.003 \)).

EGFR is an important target in NSCLC but critical to decisions regarding treatment in advanced NSCLC is identifying gene mutations within the kinase domain of EGFR. These mutations are most frequently detected in a subpopulation of NSCLC patients (female sex, non-smokers, Asians and adenocarcinoma) and are associated with increased response to EGFR tyrosine kinase inhibitors (TKIs) resulting in higher overall response rates and significantly longer progression free survival compared to chemotherapy. Unfortunately, most patients treated with EGFR TKIs progress after 7-12 months primarily because of acquired resistance through a secondary EGFR mutation known as T790M. Third generation EGFR TKIs such as osimertinib work against cells with the T790M mutation. In a recent study, osimertinib had significantly greater efficacy than platinum therapy plus pemetrexed in patients with T790M-positive advanced non–small-cell lung cancer (including those with CNS metastases) in whom disease had progressed during first-line EGFR-TKI therapy.

About 3-7% of NSCLCs have the EML4-ALK fused oncogene rearrangement and as with EGFR mutations, more likely to be found in specific populations; younger patients who are light or never-smokers with adenocarcinoma. Crizotinib is an oral small molecule inhibitor of the ALK tyrosine kinase and is associated with marked improvement in response rates and progression free survival in patients with advanced NSCLC who are found to have ALK rearrangement when compared to chemotherapy. Crizotinib is also effective (median duration of response 17.6 months and median progression free survival of 19.2 months when compared with chemotherapy in patients with NSCLC whose tumors have the chromosomal rearrangement of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase (ROS1) which occurs in about 4% of NSCLC.
One of the most exciting advances in cancer care has been the development of various strategies to enhance the immune response against cancer cells including monoclonal antibodies against the checkpoint inhibitor programmed cell death protein 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1). These strategies have led to high activity in cancer patients with long lasting responses. Nivolumab, an anti-PD-1 inhibitor, resulted in improved OS compared to docetaxel in patients with squamous cell lung cancer who had progressed on chemotherapy (median OS was 9.2 months in the Nivolumab arm (95% CI: 7.3-13.3) and 6.2 months in the docetaxel arm (95% CI: 5.1-7.3) and at 1-year, the OS was 42% for the Nivolumab group versus 24% in the docetaxel group. The hazard ratio (HR) was 0.59 (95% CI: 0.44-0.79; P=0.00025)(16). Approximately 23-28% of patients with NSCLC have a high level of PD-L1 expression (on at least 50% of tumor cells) (17). In a recent randomized trial, patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, Pembrolizumab was associated with a response rate of 58.3%, median progression-free survival of 12.5 months, and 24-month overall survival of 60.6% (18).

CONCLUSION

In the last few years, major advances have been made in the treatment of advanced NSCLC. Platinum-based chemotherapy is the standard of treatment for the majority of patients, and accurate histology is an important variable in decision making in both the selection of first line chemotherapy and when considering addition of bevacizumab. The identification of several factors, including the clinical characteristics of the patient and molecular and genetic profile of the tumor will help guide the choice of therapy. Biomarker testing is recommended for all patients diagnosed with non–small cell lung cancer and at a minimum it should include testing for EGFR mutations, fusions in ALK and ROS1, and PD-L1, because we now have approved therapies for these alterations. EGFR TKIs are first line therapy for patients with tumors harboring EGFR-mutations and when resistance develops, the tumor should be tested for T790M mutation because new TKIs are available for this mutation. Crizotinib is first line therapy for patients with ALK and ROS1 rearrangements. Immunotherapy now has a role in both second line treatment in patients who progress after systemic chemotherapy and first line in patients with increased expression of PD-L1 in tumor cells. These advances have resulted in improved survival in advanced NSCLC.

References