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Review Article

Review article on treatment of lung cancer and newer therapeutic modalities

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ABSTRACT

Introduction- lung cancer remains to be a major health problem globally leading to mortality, the cause of which is linked to chronic smoking, and other contributing factors. Staging- The American joint committee on cancer adopted the 8 th edition of the international association for the study of Lung Cancer's (IASLC) staging Chemotherapy- Several classes of anti cancer drugs based on their mechanism of action are used such as alkylating agents, anti metabolites, antibiotics, mitotic inhibitors, second and third generation EGFR inhibitors Thoracic surgery-Modern surgical techniques, like less invasive video assisted thoracoscopic surgery can be done. Also in radical radiotherapy stereotactic ablative radiotherapy is used to deliver large doses with high precision. Conclusion- immunotherapy is the most revolutionary advance in tumour research which continues to face challenges which if overcame can be an open door for multiple possibilities in the management of lung cancer.

1. Introduction

Cancer remains to be one of the major health problems in both developed and developing countries globally. Of all these types, lung cancer is the leading cause of deaths, where, chronic smoking is considered to be the major cause, in addition to the other contributing factors. Interestingly, it has been reported that men and women are equally exposed to both direct and indirect smoking. About 1.04 million cases of lung cancer are recorded each year worldwide, with the highest prevalence observed in North America and Europe. According to the available statistical data, the 5-year relative survival rate for patients having lung cancer was a mere 13% in 1975,whereas, during 1996–2003, it increased to 16%. In developing countries, the percentage of people having lung cancers is exponentially high, as more than 50% of cases belong to the local population. Lung cancer is categorised into two categories based on histological assessment, which are; i) Small-cell lung cancer (SCLC) and ii) Non-small cell lung cancer (NSCLC). In developing countries, NSCLC is very common, primarily due to smoking, and it accounts for at least 85% of cases of lung cancer, whereas, SCLC accounts for the rest of the 15% cases. NSCLC is further categorized into three sub-categories, i.e., a) Adenocarcinoma (AD), b) Large-cell carcinoma (LC) and Squamous-cell carcinoma (SQ). [1]

2. Staging

According to the 8th edition of the International Association for the Study of Lung Cancer's (IASLC) staging project 5 in January 2017, the stage groupings and are based on the new TNM ('tumour, nodes and metastases') classification

Tumour- Primary tumour subdivision is as follows: T1a <1 cm, T1b >1 to 2 cm, T1c >2 to 3 cm, T2a >3 to 4 cm, T2b >4 to 5 cm, T3 >5 to 7 cm and T4 >7 cm. Tis and T1mi

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are used for adenocarcinoma in situ and minimally invasive adenocarcinoma. Endobronchial tumours located <2 cm from the main carina were reclassified as T2 instead of T3. Similarly, T2 represents total lung atelectasis / pneumonitis. Invasion of diaphragm is considered as T4. Node- N1 depicts ipsilateral hilar lymph node, N2 depicts ipsilateral subcarinal or mediastinal lymph node while N3 depicts contralateral mediastinal or supraclavicular/scalene node. Metastases M1a, for intrathoracic metastases. Extrathoracic metastases have been reclassified into M1b represents single extra-thoracic metastasis in a one organ while M1c represents more than one extrathoracic metastases in a single organ or multiple organs. Earlier curative treatments were generally used in cases of stages I–IIIA; but in recent times the treatment of oligometastatic disease (defined as less than 5 metastases in a single organ) is an area of growing research interest.[2]

3. Chemotherapy

Chemotherapy is the use of chemicals or drugs to kill cancer cells,. Till today there are several classes of anticancer drugs which have different mechanism by which they act, and they include: a) DNA damaging alkylating agents; b) anti-metabolites which replace the normal building blocks of RNA and DNA; c) antibiotics that prevent the action of enzymes of DNA replication; d) topoisomerase inhibitors that inhibit either topoisomerase I or II, which are the enzymes involved during transcription and replication of DNA; e) mitotic inhibitors that prevent cell division; and f) corticosteroids, which are used to relieve the side effects from other anticancer drugs. Patients with inoperable and metastatic cancer may benefit from palliative chemotherapy. The recent guidelines state that first-line chemotherapeutic treatment consists of a platinum agent-based doublet, e.g. cisplatin or carboplatin in combination with a third-generation cytotoxic drug, gemcitabine and a taxane (paclitaxel, docetaxel), or vinorelbine. Meta-analyses of randomized clinical trials comparing cisplatin with carboplatin suggest that the clinical outcome of cisplatin doublets is little superior tothat of carboplatin-based chemotherapy without showing an increase in severe toxic effects. Another meta-analysis showed that there is a decrease in overall mortality in gemcitabine-platinum regimens as compared to platinum-based comparator regimens. In late 2006, bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), was approved in combination with paclitaxel and carboplatin chemotherapy for first-line treatment of patients with non-squamous NSCLC. Several anticancer drugs applied to the treatment of lung cancer (bleomycin, doxorobucin, etoposide (VP-16), cisplatin, and methotrexate) have been reported to enhance Fas ligand (FasL) expression on the surface of Fas receptor–expressing cells, suggesting that apoptosis caused by these drugs may be mediated by means of Fas cross-linking. Platinum drugs are effective for patients with a positive K-ras mutation, while a number of drugs are not useful for those with increased Her-2 expression. In addition, an increased expression of p27 enhances the efficacy of taxanes, while taxanes are not effective for cancers with a positive mutation of beta-tubulin. In conclusion, cisplatin and other platinum drugs would be of less benefit to patients with a high excision repair protein (ERCC1) expression.[3]

4. Newer Chemotherapeutic Agents

4.1. Next-generation EGFR inhibitors

Second generation- Dacomitinib is the latest second-generation EGFR inhibitor approved by the FDA for treatment of metastatic NSCLC in September 2018. It binds to Cys797 irreversibly and inhibits EGFR exhibiting exon19 deletion and L858R mutations.[4]

Third generation- In April 2018 FDA approved Osimertinib for the first-line treatment of patients with metastatic NSCLC which showed EGFR exon19 deletion or exon 21 L858R genetic rearrangements. Although it targets the T790 M mutation, it relatively spares the wildtype EGFR unlike the second-generation EGFR-TKIs. The FDA has approved osimertinib for the treatment of patients with metastatic NSCLC with T790M mutation insensitive to prior EGFR TKI therapy

4.1.1. EGFR antibodies

Necitumumab is a human, recombinant IgG1 monoclonal antibody which interacts with the EGFR through its extracellular domain. It blocks EGF-mediated receptor phosphorylation and activation of mitogen-activated protein kinases (MAPK), inducing potent antibody- dependent cellular cytotoxicity (ADCC) against tumour cells at concentrations as low as 1.0 nmol/L. It is now recommended as first-line treatment for patients with squamous NSCLC with distant organ spread, along with gemcitabine and cisplatin.[5]

4.1.2. Inhibitors of anplastic lymphoma kinase (ALK)

The ALK fusion with echinoderm microtubule-associated proteinlike 4 (EML4) has been identified as an oncogenic driver in a subset of NSCLC. The EML4–ALK fusion gene results in an oncogenic fusion protein that increases cell proliferation, differentiation and inhibits apoptosis. This is mediated through activation of the tyrosine kinase function of ALK and its downstream signalling, namely the Ras/MAPK, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/ protein kinase B (AKT) and Janus kinase (JAK)/signal transducer and transcription activation pathways. Small-molecule inhibitors of ALK kinase such as Alectinib and crizotinib are now available for ALK translocation-positive cancer.[6]

4.1.3. Inhibitors of RAF kinase

Monotherapy with Vemurafenib, a BRAF kinase inhibitor, resulted in tumour insensitivity after a certain period, probably due to BRAF mutation-independent activation of MAPK pathway. Addition of a mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor like trametinib has shown promising results in overcoming this resistance. Dabrafenib, with trametinib, was approved in June 2017 for the treatment of metastatic NSCLC with BRAFV600E mutations which are non operable. However, activation of alternative signaling pathways including PI3K/Akt, mTOR and STAT3 signalling can bypass MEK inhibition which can result in drug resistance.[7]

4.1.4. Immune check point inhibitors

Programmed cell death protein 1 (PD-1) on the surface of activated T cells interacts with its ligand PDL-1 expressed by tumour cells. The PD-1/PDL-1 complex inhibits the anti-tumour activity of the cytotoxic T cells.

Pembrolizumab is a humanized immunoglobulin (Ig) G4 kappa PD-1 monoclonal antibody, approved by the US FDA in 2015, European Medicines Agency (EMA), and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) as first-line therapy for patients with chemotherapy naïve metastatic NSCLC and high PD-L1 expression [tumour proportion score (TPS) 50%] with no EGFR or ALK genomic mutations.[8]

4.2. Thoracic surgery

Thoracic surgery is considered as the mainstay of treatment for early stage lung cancer in patients who are considered fit for surgery. Less invasive surgical methods have been developed, video-assisted thoracoscopic surgery (VATS) that have revolutionised the entire aspect of surgical fitness. Long-term survival and perioperative mortality after VATS lobectomy has been shown to be better than open surgery in some studies. A systematic review and metaanalysis found that the 5-year survival after VATS lobectomy for early stage lung cancer to be 80.1% vs 65.6% in case of open lobectomy. Video-assisted thoracoscopic surgery lobectomy also has a decreased risk of complications (29.1% VATS vs 31.7% open) and a shorter hospital stay (8.3 days VATS vs 13.3 days open). In the past ten years, surgical resection rates have increased from 9% to nearly 17% and more surgeries are being performed on people who are older than 70 years (the median age of lung cancer diagnosis is 73 years). The use of lung-sparing surgery has also increased which has decreased pneumectomy incidences where there is a mortality incidence of 11% within first 90 days. Laparoscopic robotic surgery is another area of growing interest in this field.[2]

4.3. Radical radiotherapy

Several evolving radiotherapic techniques have come forth and are used widely for treatment of carcinoma lung. Stereotactic ablative radiotherapy (SABR), developed for use in carcinoma of lung is able to deliver increased doses of radiation with a very high precision of 1–2 mm to small lesions of less than 1 cm using an external 3D coordinated system which is connected with movements during respiration. It is mainly reserved for people diagnosed with early stage cancer who are not deemed fit for surgical resection due to various comorbidities. A meta-analysis of observational studies has shown that SABR has an increased survival benefit over conventional curative radiotherapy (2-year survival 53% for conventional radiotherapy as compared to 70% with SABR).[2]

5. Conclusion

Immunotherapy is the most revolutionary advance in tumor research. This new treatment approach not only prolongs the survival of patients, but also indicates the direction for future tumor research. Immunological checkpoint inhibitors, such as PD-1/PD-L1 and CTLA-4, show an inspiring effect in melanoma, NSCLC, renal cell carcinoma, Hodgkin's lymphoma, bladder cancer and other cancers in a number of multi-center clinical trials. However, to date, its benefit remains limited to a minority of patients with certain cancer types. In addition, as a result of more successful immunotherapy treatments, we now have a significant subset of patients who initially respond, but eventually relapse. Cancer immunotherapy continues to face some challenges: (1) Deter-mining how to scientifically evaluate the efficacy of immunotherapy; (2) Determining the best strategy for tumor immunotherapy combined with other treatments; (3) Finding suitable predictors for screening the effect of ICB therapies; (4) Reducing the incidence of adverse reactions and mortality of ICB.[9]

6. Source of Funding

None.

7. Conflict of Interest

None.

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