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INTRODUCTION

Lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide, accounting for about 1.8 million new diagnoses with 1.6 million deaths every year.[1] Lung cancer can be subdivided into two main groups: non-small cell lung cancer (NSCLC), accounting for about 85% of all new lung cancer diagnoses; and small-cell lung cancer (SCLC), which represents approximately 12–15% of all diagnoses. Considering that we are in the setting of a fairly complex clinical entity, the currently available guidelines are extremely helpful in providing evidence-based guidance to physicians in their daily practice. In Europe, the main and most widely used evidence-based guidelines available are those produced by the European Society of Medical Oncology (ESMO). These are regularly updated whenever evidence supporting the implementation of new diagnostic tools, technologies, or techniques become available.[2]

SMALL-CELL LUNG CANCER

SCLC, strictly related to cigarette smoking, is characterised by a rapid doubling time, high growth fraction, and the early development of widespread metastases with a very poor prognosis. The incidence of SCLC has been falling over recent decades, likely due to the reduction in cigarette smoking rates and the routine addition of filters to cigarettes.[3] Staging of SCLC is traditionally based on the Veterans Administration Lung Study Group system, which classifies patients as having either limited-stage (LD) (disease which is limited to one hemi-thorax, with hilar and mediastinal nodes that can be encompassed within one tolerable radiotherapy portal), or extensive-stage (ED) (when disease has progressed beyond any-type limited stage) disease.[4] However, the International Association for the Study of Lung Cancer recommends applying the tumour, node, metastasis system staging to patients with LD-SCLC because it provides additional prognostic value allowing for better separation of stage-specific LD-SCLC survival curves compared with previous staging systems.[5]

Limited Disease

In LD-SCLC, median overall survival (OS) and 2-year survival rates were 15–20 months and 20–40%, respectively, with 20–25% of patients surviving 5 years.[6] The standard of care for patients with LD-SCLC is concurrent chemo-radiotherapy with early thoracic radiotherapy (with chemotherapy cycle 1 or 2). The best OS in fit patients was demonstrated with twice-daily 1.5 Gy in 30 fractions given concurrently with 4 cycles of chemotherapy. In patients who are not fit enough for twice-daily radiotherapy or are unwilling to accept increased toxic effects, treatment with a once-daily (1.8 Gy, 25 fractions) radiotherapy schedule with 4–6 cycles of concurrent cisplatin plus etoposide is recommended. This intensive approach appears to be superior to sequential chemo-radiotherapy and yields higher OS. All patients without disease progression after treatment and reasonably good performance status (PS) should receive prophylactic cranial irradiation (PCI).[7]

Extensive Disease

Despite a high objective response rate (ORR), close to 70%, outcomes of ED-SCLC patients remain poor with a median progression-free survival of only 5 months and a median OS of around 10 months. Platinum plus etoposide represents the standard treatment for patients affected by ED-SCLC and radiotherapy plays a local palliative role.[7] According to the results of an individual patient data (IPD) meta-analysis, cisplatin can be substituted by carboplatin in patients with ED-SCLC. Due to the limited number of LD-SCLC patients included in this analysis, cisplatin plus etoposide is still recommended in this group.[8] PCI should be offered to patients in a reasonably good PS with any response to first-line treatment.[7]

Although SCLC generally shows an excellent response to initial chemotherapy, most patients

ultimately relapse, for which salvage chemotherapy is an option to consider. For resistant patients with early relapse (<60–90 days after completion of first-line chemotherapy), participation in a clinical trial or best supportive care is recommended. Topotecan, either intravenous or oral, is recommended for patients having sensitive relapse, with CAV (cyclophosphamide, doxorubicin, vincristine) regimen as an alternative option. Platinum-based re-challenge, usually platinum plus etoposide, should be a further approach in very sensitive-relapsed SCLC patients.[7]

NON-SMALL-CELL LUNG CANCER

NSCLC includes squamous cell carcinoma and non-squamous histology (adenocarcinoma, and large cell carcinoma). Regrettably, the percentage of patients affected by early-stage NSCLC and suitable for radical treatment as curative intent is low. Unfortunately, most patients are diagnosed when NSCLC is metastatic and systemic therapy is the mainstay of management. However, the long-term OS of patients affected by NSCLC, both in early and advanced NSCLC stages, remains low.

Early Stages

Surgery, if feasible, should be the standard of care for Stages I and II of NSCLC, though careful evaluation is required for Stage III. Adjuvant platinum-based chemotherapy should be considered for patients with resected Stage II or III NSCLC.[9,10] An IPD meta-analysis showed that a cumulative cisplatin dose of 300 mg/m^2 delivered in 4 cycles is related to the best outcomes.[11] Cisplatin plus vinorelbine is the most frequently studied regimen and provides a superior OS benefit than other regimens; however, it is burdened with significant toxicity.[12] Thus, the selection of patients to treat with adjuvant treatment is very important to optimise results. Comorbidity, time-from-surgery, type of surgery, and post-operative recovery need to be taken into account in this decision. Post-operative radiotherapy is not recommended in radically resected NSCLC, but may be an option in Stage III based on critical evaluation of loco-regional relapse risks.[10]

Locally-Advanced Disease

Stage III NSCLC represents a heterogeneous group of patients in which cure rates and long-term prognosis differ significantly between the various sub-stages. Thus, this also contributes to the difficulty of interpreting results. In the presence of an intra-operative diagnosis of Stage IIIA-N2 disease, surgery should be followed by adjuvant chemotherapy. The addition of post-operative radiotherapy is not routinely recommended, but may be an option following individual risk assessment. Several options should be considered in patients with a pre-operative diagnosis of Stage IIIA-N2 disease: induction chemotherapy or chemo-radiotherapy, followed by surgery or concurrent definitive chemo-radiotherapy. An experienced multidisciplinary team is of paramount importance in any complex multi-modality treatment strategy decision. Concurrent chemo-radiotherapy is the treatment of choice in patients with unresectable stages IIIA and IIIB NSCLC. In the presence of conditions contraindicating concurrent chemo-radiotherapy, sequential approaches of induction chemotherapy followed by definitive radiotherapy represent a valid and effective alternative. Platinum-based regimens, particularly containing cisplatin, are the treatment of choice.[10]

METASTATIC DISEASE

In the last 10 years, improvements in the knowledge of the biological mechanisms of lung cancer have been growing, and the awareness of target molecules has led to the development of corresponding drug inhibitors. This is leading to 'personalised medicine', meaning the possibility of treating specific lung cancers with a precise genetic alteration which represents the target for a specific drug to be used in that specific individual. To date, only approximately 20% of NSCLC patients have a therapeutic drug target in clinical practice: activating mutations of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) translocations. Gefitinib, erlotinib, and afatinib are oral small molecule anti-EGFRs, strongly recommended for first-line therapy in patients with advanced NSCLC harbouring activating EGFR mutations.[13] Most patients do not present any therapeutic drug targets and the choice of first-line therapy is based on histology, comorbidity, PS, and age. In squamous NSCLC, platinum-based doublets containing taxanes, gemcitabine, and vinorelbine are considered the standard of care. In non-squamous histology two further and strongly recommended options are platinum plus pemetrexed or carboplatin plus paclitaxel plus bevacizumab (an anti-vascular growth factor receptor monoclonal antibody) regimens. In this histotype, patients who do not progress to 4 cycles of platinum-pemetrexed induction,

maintenance therapy with pemetrexed is the standard of care demonstrating an OS advantage. In elderly (age ≥70 years) and PS2 patients unsuitable for platinum-based chemotherapy, single-agent is the preferred option.[13]

According to the results of two IPD meta-analyses, cisplatin-based chemotherapy is slightly superior to carboplatin-based chemotherapy in terms of ORR and, in certain sub-groups OS is slightly superior,[14] and 4 planned cycles of first-line platinum-based chemotherapy are enough.[15]

In second-line therapy, any patient with NSCLC harbouring an ALK fusion should receive crizotinib. Second-line therapy options consist of pemetrexed for non-squamous histology, docetaxel, and erlotinib, regardless of EGFR mutational status. Erlotinib is also the only drug registered for third-line therapy, if not received previously.[13]

Recently, a Phase III randomised trial showed an impressive improvement in OS for nivolumab, a monoclonal antibody immunotherapeutic directed against the programmed death-1 receptor, when compared in second-line therapy versus docetaxel in the treatment of patients with squamous NSCLC (median OS, 9.2 versus 6.0 months, respectively).[16] Based on the results to date, nivolumab is registered for this approach.

CONCLUSION

Lung cancer is considered a 'big killer' and represents a challenging field of clinical research as many open questions remain, mainly concerning the best therapeutic approach of the disease. The knowledge of new therapeutic biological targets, such as the proto-oncogene, receptor tyrosine kinase (ROS1) rearrangements, for which crizotinib has already shown marked antitumour activity,[17] is of paramount importance to define sub-groups of patients who could benefit from 'personalised medicine'. Immunotherapy is a new frontier for the management of cancers, including lung cancer, with very promising preliminary results. The role of all professionals involved in the management of lung cancer is to keep up to date and ready to provide the best care to patients.

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