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Management of small cell lung cancer

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Abstract

Small cell lung cancer remains an important malignancy with increasing lung cancer rates in many countries. It is important to distinguish between better and poorer prognostic patient groups in order to target therapy more effectively. Modern chemotherapy usually includes a platinum combination and in selected patient groups combined modality with thoracic and prophylactic cranial irradiation. For poorer prognostic groups, treatment is less well defined and less commonly researched. Nevertheless the integration of combined modality treatments and novel drugs beckons towards an exciting avenue for future research.

1. Introduction

In the European Community lung cancer accounts for 29% of all cancer deaths. There is an increasing mortality trend from lung cancer, 10–15% increase among men every five years (except for the UK where there has been a slight decrease) and for women mortality has increased 15–30% every five years except in France, Greece and Spain where the increase has been somewhat less [1,2]. More recent data from 20 European countries describe a decrease in mortality trend up to the age of 75 years among men with the marked exception of Hungary, but with increasing lung cancer rates among women. For adults aged less than 55 years, mortality has recently peaked. However, among women, rapid increases have been seen in Denmark, The Netherlands, Hungary, Ireland and the UK, but in the latter two countries the rates have started to slow down. Lung cancer will continue to be a major cancer problem in Europe, particularly central Europe, for several decades to come unless effective tobacco control is instituted [3].

2. Prognostic groups

In SCLC, tumour extent is defined as extensive or limited stage disease. Limited stage is tumour confined to one hemithorax including the mediastinum and/or supraclavicular nodes i.e. contained within a single radiation field. Limited stage has also included ipsilateral pleural effusions in some studies. Extensive disease is more widespread tumour than contained within the limited definition. Improved accuracy of SCLC staging may be expected given the added benefit of Positron Emission Tomography in non-small cell lung cancer management [4,5]. However, studies in SCLC to date only have a small number of patients [6,7]. Moreover, there are a number of independent prognostic factors that predict survival including performance status and biochemical indices e.g. lactate dehydrogenase, alkaline phosphatase and sodium [8–11]. It is important to note that age is not a predictive factor in terms of survival prognosis. Prognostic factors should be taken into account when determining treatment strategy i.e. aiming for long-term survival or palliation with improvement in short-term survival, so as not to under-treat or over-treat patients in different prognostic groups.

3. Chemotherapy overview

Chemotherapy is the cornerstone of treatment for small cell lung cancer and active drugs include cisplatin, carboplatin, etoposide, cyclophosphamide, ifosphamide doxorubicin and vincristine. Commonly used combinations include cisplatin or carboplatin plus etoposide (PE), ifosphamide, carboplatin, etoposide with or without vincristine ICE±V, cyclophosphamide doxorubicin and vincristine (CAV), cyclophosphamide, doxorubicin and etoposide (CDE). Doxorubicin combinations are

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more commonly used in Europe whilst platinum etoposide is the treatment of choice in the US.

Data based solely on the distinction between limited and extensive stage disease in patients with good performance status (PS 0,1) have reported median survivals of 7–10 months for extensive disease and 14–20 months for limited disease, with two year survival rates in limited disease of 20–30% and 5–10% at five years. However, the overall survival in less selected groups of patients is poor at $<5\%$ at 3–5 years [12–14].

4. Modern chemotherapy

Combination chemotherapy is recommended in the majority of patients with good performance status. A number of trials in the past that have compared four drug regimens with three or two drug regimens have shown no particular differences in survival although toxicity was greater when more than two drugs were used. Furthermore there is evidence to indicate that more than six cycles of chemotherapy has no extra benefit and laterally good results have been obtained with only four cycles. Furthermore, maintenance therapy is not effective in improving survival [15,16]. In the poorer prognosis patients e.g. those with poor performance status ($PS \geqslant 2$) and extensive stage disease, concerns about the toxicity of combination intravenous chemotherapy led to a number of randomised trials to evaluate single agent oral etoposide which for many was the preferred treatment in the palliative setting. Two of the larger trials examined symptom palliation, quality of life as well as conventional survival and response rate endpoints. Both studies recruited patients with poor performance status and symptom palliation favoured intravenous combination treatment (CAV or CAV alternating with PE), as did response rate and even median survival [17,18]. Given these studies intravenous combination chemotherapy is considered to be the treatment of choice even in less fit SCLC patients In this group of patients, platinum and etoposide may be appropriate but commonly in clinical practice carboplatin etoposide is often used to avoid the fluid load diuresis required with a cisplatin regimen. Little data exist on the value of these platinum regimens in poor performance status, poor prognosis patients. However, one randomised study comparing CAV with single agent carboplatin found no major differences and in a Norwegian trial of extensive stage patients, survival and quality of life with an anthracycline regimen was no different to PE [19,20].

5. Limited stage, good performance status, better prognosis patients subgroup

Standard chemotherapy includes a variety of platinum containing regimens e.g. PE, ICE $\pm$ V. The popularity of doxorubicin containing regimens CAV, CDE, has waned over the past few years mainly due to the use of thoracic radiotherapy concurrently with chemotherapy, which prohibits doxorubicin chemotherapy given the marked doxorubicin radio-sensitisation of normal tissue, osesophagus etc. Furthermore, a recent meta analysis has indicated a slight superiority of cisplatinum based chemotherapy over non-cisplatin regimens [21]. The Norwegian study however did confirm a survival benefit of PE versus an epirubicin regimen in limited stage patients. Furthermore a recent MRC study comparing VICE chemotherapy versus CDE (and other standard regimens) recently reported a median survival of 15.1 versus 11.6 months ($P=0.026$) respectively. The difference in favour of VICE was independent of disease stage [22].

6. Combined modality treatment

A meta analysis of trials comparing chemotherapy alone with combined chemotherapy and thoracic radiotherapy found that the combined treatment improved survival in limited stage patients by 5% at three years [23] although there was no advantage for patients over 70 years of age. However, the best method of integrating thoracic radiotherapy with chemotherapy is still not completely defined. Nevertheless there has been a move recently to use thoracic radiotherapy early with chemotherapy i.e. with course 1 or 2 rather than at the end of chemotherapy. The definitive study was from Canada where PE in combination with radiotherapy starting with cycle 2 was superior to concurrent radiotherapy beginning with cycle 6 [24]. This remains the only study where there is a statistically significant survival difference. Nevertheless when the Canadian trial was replicated by the London Lung Cancer Group, no survival difference was found for early versus later radiotherapy [25]. The Turrisi study which compared twice daily with once daily fractionation, with radiotherapy delivered concurrently on course one of four cycles of PE gave a two year survival rate of 26 versus 16% in favour of twice daily fractionation [26]. Nevertheless there are still questions about the timing of radiotherapy in conjunction with chemotherapy, the dose to be used and the fractionation regimen [27–31]. The mechanism of these beneficial radiation effects is thought to be due to early reduction of drug resistance clones developing in the chest tumour. However, the ability to deliver the newer fractionation regimens and higher total doses of radiotherapy is constrained by machine time and staffing issues in many hospitals. There is also a role for prophylactic cranial irradiation (PCI) in patients who have undergone a complete systemic remission. The survival benefit is the same as that achieved with consolidation thoracic radiotherapy [32]. Prospective studies have shown no evidence of neuropsychological sequelae [33]. Indeed

SCLC patients have neuropsychological abnormalities present before the start of PCI with no detectable decline in status up to two years after the start of the cranial irradiation [34,35].

There is a need to develop better chemotherapy regimens given the systemic nature of SCLC. A variety of strategies have been employed, namely maintenance treatment alternating different chemotherapy regimens i.e. PE/CAV etc., but these have not been successful. However, if dose intensity in good prognosis patients is increased (accelerated chemotherapy with shortened cycle intervals) and dose reduction is avoided, there has been improvement in survival over standard treatment in several randomised trials [36]. When the CDE regimen was used, a statistically significant small increase in median survival was found in the MRC study with accelerated chemotherapy every two weeks with G-CSF compared with standard three week interval [37]. However, in the recent EORTC study which had a more complicated factorial design and other differences from the MRC study, no significant difference was observed [38]. The series of trials has been reviewed by Tjan-Heijnen [39].

7. Salvage chemotherapy and new agents

Survival following relapse from first line chemotherapy is generally poor with a median value of around four months [40]. Nevertheless these groups of patients can be separated into sensitive and resistant groups to subsequent chemotherapy based on their initial response to chemotherapy and the progression free interval [16,41]. Radiotherapy can also provide palliation but this may not be possible to the chest if consolidation thoracic radiotherapy had been given previously in initially limited stage patients. Another approach in sensitive patients who have responded and who have had a relapse free interval of at least three months is to re-induce with the same first line regimen. However, this may not be possible due to the preceding chemotherapy with reduced tolerance to toxicity etc. Although the PE regimen can produce further responses in patients treated with previous CAV therapy (about half), the results with CAV salvage following PE are less impressive—50% compared with 20% [15,40,41].

New drugs have been examined within clinical trials in this situation including topotecan which has shown benefit in terms of symptom control with equivalent survival and response rate to a CAV regimen in the treatment of recurrent SCLC [42]. An oral preparation is now being examined and should show advantages in terms of convenience and possibly reduced toxicity [43].

Extensive stage patients for whom current treatment has not produced long-term survival are also candidates for new drug evaluations. Chemotherapeutic agents have included the taxanes, topoisomerase 1 inhibitors, gemcitabine and vinorelbine [15,44]. An interesting study from Japan compared irinotecan with cisplatin versus cisplatin and etoposide in extensive stage patients. The study was stopped early after the equivalent of 154 out of 230 patients on the basis of a significant difference in median survival ($P = 0.002$) 12.8 months versus 9.4 in favour of the irinotecan arm [45]. Similar studies are being repeated both with irinotecan and the other topo 1 inhibitor, topotecan. A variety of other agents are being examined including thalidomide, third generation platinum drugs and molecular targeted strategies [44].

8. Conclusion

There has been perhaps a loss of focus in small cell lung cancer given the advent of more successful treatment in non-small cell lung cancer. It is important to emphasise however, that small cell lung cancer is a very chemosensitive tumour and the newer methods of integrating chemoradiotherapy together with new drug development hold considerable promise for the future.

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