SMALL CELL LUNG CANCER UPDATE

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Abstract

Small cell lung cancer remains a highly lethal form of cancer, with few advances made in treatment over the last two decades. The use of platinum-containing doublet chemotherapy, and concurrent chemotherapy and thoracic irradiation in limited stage disease, remains the standard of care. To date, a number of trials have been conducted to assess the impact of newer chemotherapy agents, either for single agent activity or combined with standard chemotherapy, but with limited success. Many of the recent benefits seen in other forms of cancer (including non-small cell lung cancer) arise from the identification and targeting of specific molecular abnormalities that promote cancer growth and spread. However, although a range of targeted therapies have also been trialled in small cell lung cancer, and despite promising in-vitro data, these have not as yet produced major breakthroughs in clinical management. Further elucidation of the molecular mechanisms in small cell lung cancer and therapies directed at these abnormalities holds the key to improving outcomes in this condition, but requires significant ongoing work.

Small cell lung cancer (SCLC) accounts for 10-20% of all lung cancer, and is characterised by a high growth fraction, rapid doubling time and early metastatic spread. Despite being highly sensitive to chemotherapy and radiotherapy, five year survival rates remain dismal for this disease, and have altered little over time. Concurrent chemotherapy and thoracic irradiation has been used for limited stage disease for many years, and platinum based doublet chemotherapy has been the standard of care for extensive stage disease for decades. Avenues of investigation for new treatment options have included alternate chemotherapy agents, both alone and in combination with standard chemotherapy regimens, and targeted treatments. These strategies, many still in their early days, have yet to provide the benefits hoped for in SCLC, but provide some optimism for improved outcomes in the future.

Current treatment

Staging

The division of SCLC into limited and extensive stage disease has been the standard classification used since the 1960s.[1] More recently, TNM classification of SCLC has been proposed by the International Association for the Study of Lung Cancer and is used in the American Joint Committee on Cancer 7th edition of 2010.[2] In this new system, M1 (with any T and N stage) denotes extensive disease, with limited stage disease defined as any T and N stage with no identified metastases (excluding T3 - T4 disease with multiple lung nodules that cannot be encompassed in one radiotherapy field and is therefore considered extensive stage disease). The TNM staging system has been shown to have prognostic value, with a statistically significant inverse association between increasing T stage and survival, and a similar relationship with increasing N stage.[3] This staging system may help to better stratify patients in clinical trials of limited stage disease, but as yet is unlikely to change clinical decision making.

The use of PET scans in the evaluation of SCLC is also improving the accuracy of staging and the planning of treatment. Due to the highly metabolic nature of SCLC, PET scans can provide valuable information that may downstage, or more commonly upstage, disease.[4] This can be useful in tailoring treatment, including radiotherapy planning in limited stage disease, or altering management plans for those found to have extensive stage disease.

Limited stage disease

Surgery may be appropriate for the very small number of patients (2-5%) who present with stage 1 disease, with consideration of adjuvant chemotherapy post operatively. The role of surgery has historically been unclear beyond stage 1 disease, with a lack of robust prospective trial data. A randomised Medical Research Council trial in the 1970s suggested that there was no benefit to surgery compared to radiotherapy in limited stage disease, although few early stage patients (T1-T2) were included.[5] More recent retrospective case series have suggested that surgery may be beneficial in appropriately selected patients, particularly with the improved ability for accurate staging now possible. For example, a retrospective series of 1415 patients reviewed at the Johns Hopkins Medical Institutions suggested a benefit for surgery in conjunction with chemotherapy in selected patients with early stage SCLC.[6] Review of the SEER database appears to confirm this observation in those with local disease only,[7] but is limited by the lack of information about subsequent treatment. It may be that surgery has a role in combination with neoadjuvant or adjuvant chemotherapy, but this needs to be further elucidated in prospective randomised trials.

Concurrent chemotherapy and thoracic irradiation remains the standard of care for higher stage limited disease that is encompassable in a radiotherapy field. Doublet chemotherapy containing a platinum agent in combination with etoposide is routinely used, with concurrent thoracic irradiation which may be given in a hyperfractionated format. The response rate ranges from 70 to 90%, with

median survival of 14 - 20 months. Prophylactic cranial irradiation is recommended in those with complete response to treatment, with evidence from a meta-analysis that this strategy both decreases the development of brain metastases and prolongs survival.[8]

Despite initial responsiveness to chemotherapy, almost all patients will relapse and die of their disease. Median survival in those treated with second line chemotherapy is in the order of four to five months. A proportion of patients also demonstrate resistant disease, or relapse early (within three months of treatment). These patients do particularly poorly with second line chemotherapy, with response rates usually less than 10%.

With no clear evidence for the superiority of any one regimen, options for therapy include retreatment with platinum based chemotherapy for those who relapse more than three months from completion of prior treatment, where response rates to second line treatment are in the order of 25%. Other possible management strategies include the use of CAV (cyclophosphamide/doxorubicin/vincristine), or topotecan in oral or parenteral formulation. Topotecan has been shown to be better than best supportive care in terms of progression free and overall survival in a phase 3 study,[9] and a phase 3 trial found it had similar survival outcomes to CAV (although topotecan did demonstrate better outcomes for symptom relief).[10] Clinical trial enrolment, if available and appropriate, remains an important consideration for such patients.

Extensive stage disease

Platinum-based doublet chemotherapy has been recommended as first line treatment for extensive stage SCLC for decades. Cisplatin or carboplatin in combination with etoposide, has become the mainstay of treatment based on two randomised control trials that suggested there was a survival benefit to this approach. Cisplatin and carboplatin appear to be similar in terms of efficacy, based on a metanalysis of four randomised trials in extensive and limited stage disease, with carboplatin frequently used for ease of administration and differing toxicity profile.[11]

Response rates for chemotherapy are generally in the order of 50 - 80%, with up to 30% obtaining a complete response. For those who demonstrate a response to chemotherapy, PCI should be considered based on evidence from a phase 3 study, which showed the one-year survival rate was 27.1% (95% CI, 19.4–35.5) in the radiation group and 13.3% (95% CI, 8.1-19.9) in the control group.[12] Consolidation thoracic irradiation may be appropriate for selected patients who respond well to chemotherapy, with evidence for decreased chest recurrences and prolonged survival with its use in a trial of those with extensive stage disease who had an excellent response to initial chemotherapy.[13] The patients randomised to receive radiation therapy had an improved survival, with five year survival of 9.1% compared to 3.7% (p=0.041) in those who received further chemotherapy alone. This finding is now being tested in a randomised prospective trial by the Dutch Lung Cancer Study Group (the CREST trial).

Palliative radiation therapy is also often used for painful bony metastases, established brain metastases, and other symptomatic complications in patients who have relapsed after chemotherapy.

New directions in treatment

Chemotherapy

Given the chemosensitivity of SCLC, the addition of a third chemotherapy agent to the standard platinum and etoposide combination has been explored in a number of studies. Paclitaxel in this setting showed no benefit in survival (but an increase in toxicity) in two studies.[14,15]

Newer agents have also been investigated in trials comparing these to standard chemotherapy. Trials in the Japanese population have shown promising results with the use of cisplatin and irinotecan in combination. The phase 3 Japanese Clinical Oncology Group 9511 showed a significant overall survival benefit for cisplatin/irinotecan when compared to cisplatin/etoposide (12.8 v 9.4 months, p=0.002),[16] but these results were not able to be replicated in the non-Japanese population, with no difference found in two larger randomised phase 3 trials.[17,18] It is hypothesised that the differing outcomes between the Japanese study and the subsequent US studies, and the dissimilar rates of adverse events noted (particularly diarrhoea and neutropenia), may be due to genotypic variations in these groups.[19]

The combination of cisplatin and topotecan has been shown to be at least as good as cisplatin and etoposide, but with a differing adverse event profile, including haematological toxicities, when parenteral topotecan is used.[20] Topotecan has also been investigated as a maintenance agent following benefit from cisplatin and etoposide therapy, but did not show a benefit in this setting.[21]

Amrubicin is licensed in some countries, such as Japan, for use in combination with a platinum agent for the treatment of small cell lung cancer. Amrubicin is a synthetic anthracycline, with promising data, including showing a response rate of 88.6% (95% CI 75.4% - 96.4%), with a median survival of 13.6 months (95% CI 11.1 - 16.6 months) when used in combination with cisplatin in a phase 1 - 2 trial.[22] These findings prompted a phase 3 trial of amrubicin with cisplatin compared to irinotecan and cisplatin, which showed that the amrubicin containing doublet was not equal to irinotecan and cisplatin.[23] The combination of amrubicin and irinotecan in a phase 1 study proved to be intolerable due to the significant rate of haematological toxicity, particularly neutropaenia.[24]

Temozolomide has been shown to have some activity in a phase 2 study of SCLC, particularly in those with brain metastases. A single arm study by Pietanza et al showed a 20% objective tumour response rate (in a mixed population of patients with relapsed sensitive or refractory disease), with a 19% response rate in those receiving 3rd line treatment, a group for whom no standard therapy exists.[25] This study also found that a larger number of cases with methylated O6-methylguanine-DNA methyltransferase (MGMT) had responses to treatment compared to those with unmethylated MGMT, suggesting a subgroup of patients who may have greater benefit from temozolomide.

Targeted therapies

Given the success in other cancer types, and with limited success with new chemotherapeutic agents, attention has also turned towards identifying the molecular abnormalities present in SCLC that may be targets for personalised therapy.

SCLC is known to be highly angiogenic, with significantly higher levels of VEGF found in those with SCLC than healthy controls,[26] although there is mixed evidence for its prognostic value.[27,28] This information has lead to the trial of established antiangiogenic treatments that have proved beneficial in other cancer types. Single arm phase 2 trials conducted by the Eastern Co-operative Oncology Group,[29] and the CALGB,[30] have shown a modest improvement in progression free survival, consistent with the findings of the SALUTE randomised phase 2 trial, but no significant survival benefit and no strong signal to warrant progression to a phase 3 trial.[31] Aflibercept, a VEGF trap, has been tested in a phase 2 South West Oncology Group study in combination with topotecan and showed an improved disease control rate, but no survival differences when compared to topotecan alone.[32] Thalidomide has also been studied, but has not been found to be beneficial in a number of trials, including a randomised trial of 724 patients with limited and extensive stage disease in combination with chemotherapy, where there was no benefit in either progression free survival or overall survival.[33]

Trials of tyrosine kinase inhibitors with antiangiogenic properties have also not proved to be successful to date, with particular note made of the high levels of toxicity with these agents when used with chemotherapy. Both sunitinib and sorafenib have been investigated in phase 2 studies, with single agent treatment not found to be beneficial.[34,35] A small phase 2 trial has shown some benefit for sunitinib when used as maintenance therapy following first line chemotherapy,[36] but these results have not yet been validated in a phase 3 study. Sorafenib in combination with chemotherapy and as maintenance, despite showing some anti-tumour activity, produced too many adverse effects to be considered suitable for ongoing studies.[37] A trial of vandetanib used in the maintenance setting following response to first line chemotherapy did not show any benefit over placebo,[38] and similarly cediranib failed to show benefit in relapsed or refractory SCLC.[39]

Matrix metalloproteinases have also been targeted for therapy in small cell lung cancer. These are proteolytic enzymes that can act on the extracellular matrix to affect the tumour microenvironment. They are upregulated in almost all human cancers, and can promote cancer progression by influencing cell growth, migration and invasion, angiogenesis and metastasis. The matrix metalloproteinases inhibitors tanomastat and marimastat have been evaluated for a prospective role as maintenance therapy in those who had responded to first line therapy based on this finding, but no significant improvement was found compared to placebo treatment in either trial.[40,41]

There has been some evidence that a very small proportion of SCLC may harbour an EGFR (epidermal growth factor receptor) mutation (up to 4% in the analysis of 122 specimens from a Japanese centre.[42] These were found predominantly in mixed histology tumours that demonstrated both adenocarcinoma and SCLC cells. A small phase 2 study using gefitinib in unselected patients with chemosensitive and chemorefractory disease failed to show activity, likely due to the low rate of EGFR mutations.[43]

With in vitro evidence for the role of functional c-kit receptors in some small cell lines and inhibitory effects of imatinib,[44] human trials have been undertaken but have failed to show benefit. A phase 2 trial of 19 patients, hampered by the finding that kit positivity in tumour samples was significantly lower than hypothesised (21 v 70%), showed no anti-tumour effect from imatinib.[45] Subsequent phase 2 studies of imatinib in patients selected for the presence of tumour c-kit protein expression failed to demonstrate any clinical activity in spite of patient selection, suggesting that target expression may not provide the answer to developing new targeted agents in this condition.[46,47]

Bcl-2 has also been an attractive target for attention in this disease. It is overexpressed by many tumours (including many SCLCs),[48,49] and overexpression is linked to chemotherapy resistance through bcl-2's regulation of the intrinsic apoptotic pathway. In vitro models have shown an increased efficacy of cisplatin and etoposide chemotherapy when used with an antisense oligonucleotide directed to bcl-2 mRNA.[50] Based on these findings, oblimerson, an antisense oligonucleotide, has been studied in combination with carboplatin and etoposide in a phase 2 randomised trial, but failed to show a benefit in objective or complete response rates, and demonstrated no survival benefit.[51]

Mutations in p53, RB1 and PTEN that may increase the susceptibility of SCLC cells to DNA damage and allow for synthetic lethality upon exposure to a PARP (poly(ADP-ribose) polymerase) inhibitor, have also been shown in SCLC.[52,53] In vitro, SCLC lines show sensitivity to PARP inhibition that is similar to that of BRCA-1 and PTEN mutated breast cancer lines, and a synergistic effect with the addition of chemotherapy,[54] suggesting this may be a novel strategy for tumour targeting. Trials are currently underway of PARP inhibitors in combination with chemotherapy in SCLC to further investigate the effectiveness of this strategy.

Conclusion

Despite ongoing work, the prognosis for patients with SCLC remains grim. Many agents have shown promising early results that did not translate into clinical benefits in subsequent trials, or proved to have significant adverse events that limited their utility. There is hope that ongoing research and further elucidation of the molecular abnormalities that drive SCLC may lead to new avenues of therapy for small cell lung cancer, a malignancy which is in desperate need of more effective and durable treatments.

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