A systematic review of survival following anti-cancer treatment for small cell lung cancer

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Summary Message: This is a comprehensive analysis of early and late survival following treatments recommended by the European Society of Medical Oncology for small cell lung cancer. Our survival benchmarks can inform the treatment selection process going forward.

Abbreviations

SCLC- Small cell lung cancer

ESMO- European Society of Medical Oncology

PCI- Prophylactic cranial irradiation

LD-SCLC- Limited stage small cell lung cancer

RCT- Randomized controlled trial

ED-SCLC- Extensive stage small cell lung cancer

PS- Performance status

CI- Confidence interval

Abstract

Objectives

We conducted a systematic review and meta-analysis of survival following treatment recommended by the European Society of Medical Oncology for SCLC in order to determine a benchmark for novel therapies to be compared with.

Materials and Methods

Randomized controlled trials and observational studies reporting overall survival following chemotherapy for SCLC were included. We calculated survival at 30 and 90-days along with 1-year, 2-year and median.

Results

We identified 160 for inclusion. There were minimal 30-day deaths. Survival was 99% (95%CI 98.0-99.0%, $I^2$33.9%, n=77) and 90% (95%CI 89.0-92.0%, $I^2$79.5%, n=73) at 90 days for limited (LD-SCLC) and extensive stage (ED-SCLC) respectively.

The median survival for LD-SCLC was 18.1 months (95%CI 17.0-19.1%, $I^2$77.3%, n=110) and early thoracic radiotherapy (thoracic radiotherapy 18.4 months (95%CI 17.3-19.5, $I^2$78.4%, n=100)) vs no radiotherapy 11.7 months (95%CI 9.1-14.3, n=10), prophylactic cranial irradiation (PCI 19.7 months vs No PCI 13.0 months (95%CI 18.5-21.0, $I^2$75.7%, n=78 and 95%CI 10.5-16.6, $I^2$81.1%, n=15 respectively)) and better performance status (PS0-1 22.5 months vs PS0-4 15.3 months (95%CI 18.7-26.1, $I^2$72.4%, n=11 and 95%CI 11.5-19.1 $I^2$77.9%, n=13)) augmented this. For ED-SCLC the median survival was 9.6 months (95%CI 8.9-10.3%, $I^2$95.2%, n=103) and this improved when irinotecan+cisplatin was used, however studies that used this combination were mostly conducted in Asian populations where survival was better. Survival was not improved with the addition of thoracic radiotherapy or PCI.

Survival for both stages of cancer was better in modern studies and Asian cohorts. It was poorer for studies administering carboplatin+etoposide but this regimen was used in studies that had fewer patient selection criteria.

Conclusion

Early thoracic radiotherapy and PCI should be offered to people with LD-SCLC in accordance with guideline recommendations. The benefit of the aforementioned therapies to treat ED-SCLC and the use of chemotherapy in people with poor PS is less clear.

Keywords

Epidemiology

SCLC survival

Chemotherapy

Radiotherapy

30-day survival

Introduction

The European Society of Medical Oncology (ESMO) recommend 4-6 cycles of cisplatin or carboplatin doublet chemotherapy as first-line treatment for all stages of SCLC.(1) Thoracic radiotherapy can be given concurrently, in fitter individuals with limited stage (LD-SCLC), or sequentially to people who have responded to initial chemotherapy. Prophylactic cranial irradiation (PCI) is generally reserved for people who have responded to chemotherapy. These treatments have remained unchanged for 30 years but novel therapies are emerging. Immunotherapies such as atezolizumab (IMPOWER-133 trial) and durvalumab (CASPIAN), in combination with chemotherapy, have shown increases in the median survival of approximately 2 and 3 months respectively when compared to chemotherapy alone.(2, 3) Both these treatments have been given approval for use in extensive stage SCLC (ED-SCLC) by the US Food and Drug Administration. However, these new treatments are expensive and the U.K. list price for one vial of atezolizumab is approximately £3,800.(4) Hence, in order to assess whether these novel treatments are economically viable a comprehensive survival assessment of the existing therapies is needed. This will ensure that the claimed survival advantages of immunotherapy are accurate.

Similarly, in order to maximise the efficacy of current treatments patients must be selected appropriately. Deaths occurring early after chemotherapy (within 30-days) are a measure of poor selection, but the evidence base for this in SCLC is limited.(5) Hence, the objectives of this study are to examine early and late survival by ESMO recommended treatments for SCLC in order to increase this evidence base and inform the appraisal process of novel treatments.

Methods

Search strategy

We searched EMBASE, MEDLINE and electronic search engines for English language randomized controlled trials (RCTs) or observational cohort studies which reported overall survival following

receipt of cisplatin or carboplatin in combination with etoposide, irinotecan or topotecan for SCLC. The search strategy can be found in *Supplement 1*. Our search was conducted on 7th June 2016. After the initial search we examined the archives of the European Society of Medical Oncology, American Society of Clinical Oncology and the International Association for the Study of Lung Cancer for conference abstracts. We searched the references of included manuscripts. The search was completed on the 22nd November 2017.

Inclusion Criteria

The inclusion criteria are presented in *Supplement 2* and were applied based on the study protocol published in the manuscript. We examined overall survival in treatment naïve individuals with SCLC who received platinum based chemotherapy in-keeping with ESMO guidelines.(1) Studies were excluded if "up front" prophylactic growth colony stimulating-factor or antibiotics were given before the first chemotherapy cycle as these are not routinely recommended in SCLC in the U.K.(6) If a study protocol was changed throughout its duration and this was not compatible with our inclusion criteria it was excluded. Abstract only publications were included. Manuscripts with duplicate study populations were used once, with the most up to date publication being included. Two reviewers (GJ, TM) applied the inclusion criteria, if there was disagreement a third was consulted (DRB or RBH) and a consensus was reached.

Data extraction

Three reviewers extracted data (GJ, KE, TM) consisting of trial design, participant characteristics, treatment schedule, survival (30-day, 90-day, 1-year, 2-year and median survival), cause of 30-day death and quality score. We used graph digitalizer software, Digitizelt V2.2, (Braunschweig, Germany) to extract survival data from Kaplan Meier plots if survival data was not within the text.(7-9) Extracted values were crosschecked for accuracy. Our quality score combined the Cochrane risk of bias and Newcastle-Ottawa scoring methods (found in *Supplement 3*) to assess survival reporting and study design. RCTs and cohort studies could achieve a maximum score of 30 and 27 respectively.

Statistical Analysis

All analyses were carried out using STATA V15 (TX, USA). We derived pooled survival estimates from individual treatment arms. For example, a study with two treatment regimens meeting our inclusion criteria would have two survival outcomes in our meta-analysis. We calculated a pooled survival estimate at: 30-days, 90-days, 1-year and 2-years using a random effects model allowing for Freeman-Tukey arcsine transformation to stabilize variances between studies.(10) The median survival estimate was produced from a random effects inverse-variance method (DerSimonian Laird).(11) Heterogeneity was quantified using the I^2 statistic.(12) In studies where the median survival was presented without 95% confidence intervals (CI), we used a method by *R.P Jones et al* to estimate variance and 95%CIs.(13) We conducted a sensitivity analysis without these estimated values.

Combined stage, LS-SCLC and ED-SCLC pooled survival estimates (with 95%CIs) were presented separately. Estimates were stratified by study factors and interventions. Studies were grouped by quality score; (poor (0-9), moderate (10-14), good (15-19) and very good (20-27)). Study design was classed as RCT or cohort. The study year and median participant age were divided into 10-year groups. The study region was the continent where it was conducted and broadly represents the ethnicity of the cohort. Performance status (PS) was derived from inclusion criteria and divided into 0-1 to 0-4. Mixed/alternating chemotherapy regimens were grouped into: platinum+etoposide (cisplatin/carboplatin+etoposide) and platinum+etoposide/irinotecan (cisplatin/carboplatin+etoposide/irinotecan). Thoracic radiotherapy, if given, was grouped according to the start time (before (early) or after (late) the third chemotherapy cycle).

Results

Search process

We identified 10,487 titles and after screening 130 remained. Another 30 studies were identified from references of included manuscripts giving a total of 160 studies. *Figure 1* is a flowchart of this process.

Summary of studies

In total, we examined survival data from 22,528 people. *Supplement 4* summarises the included manuscripts, 11 of which were abstracts.(14-174) The majority of manuscripts were observational cohort studies (100 (62.5%)) and the remaining were randomized/non-randomized controlled trials (60 (37.5%). The earliest commenced in 1981, however, most were from 2000-2009 (67(41.9%)). Many studies were from Asia (60 (37.5%)) followed by Europe (45 (28.1 %)) and North America (36 (22.5%)). The average, median participant age was 63 years (SD 5.3 years) and most were male (median proportion 78.9%). Studies mainly consisted of people with PS 0-2 (107 (66.9%)) and 31 (19.4%) had minimum life expectancy criterion ranging from >8 weeks to >6 months. Other inclusion pre-requisites were adequate bone marrow, hepatic and renal function. Common exclusion criteria were pleural/pericardial effusions, cardiovascular disease and symptomatic brain metastases.

The median quality score for cohort studies was 18.5/27 (IQR 15.5-20.5, range 7.5 to 24 (34, 145)) and 18.5/30 (IQR 17.25-19.75, range 10 to 19 (112, 148)) for RCTs. The causes for poorer quality were lack of reporting of early survival and cause of early death.

Thirty day survival

The 30-day survival for LD-SCLC studies was 100% (95% CI 100%, I^2 0%, n=76) and for ED-SCLC it was 96% (95% CI 95-97%, I^2 67.3%, n=71). These varied minimally by study factors and are reported in *Supplement 5*. We identified 31 studies where 75 people died within 30 days of chemotherapy and the cause of death was published (summarized in *Supplements 6 & 7*.) The majority of deaths were

attributed to neutropenic sepsis (n=27 (36.0%)), disease progression (n=11 (14.7%)) and cardiovascular, gastrointestinal and others (n=8 (10.7%) in each).

Ninety day survival

Table 1 demonstrates survival at 90 days stratified by study factors. Survival was 99% (95%CI 98-99%, $I^2$33.9%, n=77) for LD-SCLC and varied minimally by study factors (*forest plot Supplement 8*).

Survival was shorter in ED-SCLC (90% (95%CI 89-92%, $I^2$79.5%, n=73, *forest plot Supplement 9*). Survival improved in recent studies (2010-2015 96% (95%CI 89-99%, $I^2$81.6%, n=7)) and in Asian cohorts (97% (95%CI 95-98%, $I^2$42.8%, n=26)). Carboplatin+etoposide and cisplatin+topotecan had the poorest 90-day survival (88% (95%CI 83-92%, $I^2$77.3%, n=14) and 86% (95%CI 83-89%, $I^2$27.9%, n=35) respectively). Worse PS heralded lower 90-day survival (PS 0-4 87% (95%CI 74-96%, $I^2$92.7%, n=9)).

Late survival

We report late survival at 1-year (demonstrated in *Table 2*) and this varied considerably by stage. The 1-year survival for LD-SCLC was 73% (95%CI 70-75%, $I^2$74.0%, n=91, *forest plot Supplement 10*). This was better with Asian cohorts (79% (95%CI 75-82%, $I^2$60.9%, n=37)), receipt of irinotecan+etoposide (77% (95%CI 66-86%, $I^2$62.6%, n=7), young age (74% (95%CI 69-79, $I^2$61.7%, n=20)), early thoracic radiotherapy (77% (95%CI 73-80%, $I^2$68.0%, n=40) and PCI (75% (95%CI 72-77%, $I^2$74.1%, n=69)).

One-year survival for ED-SCLC was 38% (95%CI 35-40%, $I^2$74.9%, n=80, *forest plot Supplement 11*). This has improved with time (2010-2015 55% (95%CI 43-68%, $I^2$83.9%, n=7) vs 1980-1989 28% (95%CI 24-33%, $I^2$45.4%, n=15)). In addition, Asian cohorts (47% (95%CI 42-52, $I^2$72.9%, n=31)) and irinotecan+cisplatin (49% (95%CI 43-54%, $I^2$70.6%, n=15)) had better survival. Survival was not significantly different with age, PS or with the addition of thoracic radiotherapy and PCI.

The 2-year survival for LD-SCLC was 41% (95%CI 38-44%, $I^2$78.9%, n=85) and for ED-SCLC it was 9% (95%CI 7-10%, $I^2$67.5%, n=66). On the whole, there was significant variation in survival by the same study factors as those at 1-year. Hence, we have not presented these results in full. The table of results can be found in *Supplement 12*.

Median survival

The results of median survival are shown in *Table 3*. For LD-SCLC survival was 18.0 months (95%CI 17.0-19.1, $I^2$77.3%, n=110 (forest plot *Supplement 13*)). This was longer with modern studies, Asian cohorts, better PS, young age, receipt of thoracic radiotherapy and PCI.

For ED-SCLC median survival was 9.6 months (95%CI 8.9-10.3, $I^2$95.2%, n=103 (forest plot *Supplement 14*)). This was better for studies that gave irinotecan+etoposide, had Asian cohorts and included people with good PS.

The aforementioned results showed significant heterogeneity and this was not reduced by the sensitivity analysis (studies with estimated 95%CIs removed) however, the conclusions remained the same.

Discussion

Main Findings

There were few deaths within the 30 days of the first chemotherapy dose and these were predominantly due to neutropenic sepsis. Early survival was similar across all ages but this changed at 1-year for LD-SCLC, where the elderly were less likely to survive, most likely a result of attrition bias. Long term survival varied considerably by stage and was better in Asian cohorts and recent studies that included people with good PS. Thoracic radiotherapy and PCI augmented median survival in LD-SCLC.

Strengths

To our knowledge, this is the largest systematic review conducted in SCLC. Quantifying early and late survival permits a better understanding of the early mortality risks of treatment vs the long-term survival gains, allowing better informed treatment choices and patient selection. The large number of included studies means our results are less prone to publication bias unlike other, smaller, systematic reviews.(175-177)

Limitations

In this study some factors, such as PCI and radiotherapy, do not consist of all the individuals who received these treatments as we categorised this variable from the study protocol. This grouping method was needed as there was significant heterogeneity in study design and reporting. However, our results are consistent with other literature. Our results do not fully represent "real world survival" as many patients in clinical practice do not meet trial inclusion criteria. However, we have included observational studies that have far less selection criteria than RCTs.

Comparisons with other research

Early survival

The evidence base for early mortality and its causes following chemotherapy is limited. The proportion of treatment related deaths, defined as death related to and within 4 weeks of completion of chemotherapy, was found to be 2.95% in a systematic review of phase III SCLC trials.(178) Neutropenic sepsis was found to be the leading cause of these. Conversely, observational research from England found that 30-day mortality for palliative and curative chemotherapy for SCLC was 12% and 4% respectively.(5) Our findings lie between these two studies as we have included clinical trials and observational studies.

Chemotherapy and cohort ethnicity

Irinotecan+cisplatin tended to have better survival in comparison to cisplatin/carboplatin+etoposide and there are several explanations for this. First, carboplatin+etoposide regimens were more commonly used in studies that recruited patients with worse PS and more comorbidities, biasing carboplatin to poorer outcomes. Indeed, when the efficacy of cisplatin and carboplatin were compared in a systematic review of individual patient data there was no difference between the two (median overall survival 9.6 months and 9.4 months for cisplatin and carboplatin respectively). (179) Second, the majority of irinotecan containing studies have been conducted in Asia where it has more favourable outcomes.(175) However, outside of Asia there is limited evidence for its superiority over etoposide.(180) Indeed, a systematic review that included many of the same Asian, irinotecan studies as ours concluded that irinotecan augmented survival by 1-2 months compared to platinum+etoposide.(175) Contrastingly, a study in Caucasians found no differences in survival between etoposide and irinotecan containing chemotherapy.(180) The variation of irinotecan metabolism between ethnic groups is well documented and approximately 10% of Caucasians have a variant form of the UDP-glucuronosyltransferase 1 polypeptide A1 enzyme. This variant enzyme leads to poorer metabolism and subsequently irinotecan toxicity.(181) (182)

The prevalence of SCLC amongst never-smokers is greatest in Asia and the augmented survival of Asian cohorts is likely a reflection of different SCLC aetiological exposures.(183) Indeed, evidence suggests that never-smokers with SCLC have better survival than ever-smokers.(184, 185) This observation is most pronounced in Asian females who have greater exposure to indoor air pollution from cooking oils rather than tobacco.(186) Similarly, genetic analysis of SCLC histological samples from never-smokers have shown a greater burden of oncogene driver mutations (such as EGFR) than in ever-smokers raising the concept of SCLC in never smokers being a distinct disease.(185) Other confounders to our findings are the study design and inclusion criteria.

Study year

We found survival was shorter in older studies. *Schabath et al* drew similar conclusions when they compared the survival of two cohorts of people with SCLC treated at a single centre between 1986-1999 and 2000-2008.(187) The median overall survival was significantly better in the 2000-2008 cohort (11.3 months (95% CI 10.5-12.7)) in comparison to the 1986-1999 group (15.2 months (95%CI 13.6-16.6)). This increase was attributed to greater use of multi-modality therapy rather than chemotherapy alone and less use of cyclophosphamide, doxorubicin and vincristine combination treatment. In addition, the better selection of patients and improved healthcare practices e.g. infection control awareness, also explain our results. (25, 28, 41) (46, 142, 166, 167) (188). Lastly, improved methods for early detection and staging have caused a modest stage migration over time. This migration towards earlier stage subsequently improves overall survival, the so-called Will Rogers phenomenon. Indeed, the aforementioned study had greater proportions of LD-SCLC during 2000-2008 (50.3%) in comparison to 1986-1999 (40.0%).

Thoracic radiotherapy

In-keeping with treatment recommendations, early radiotherapy in LD-SCLC augmented survival. A seminal meta-analysis of 7 RCTs demonstrated improvement in 2 and 3 year survival with thoracic radiotherapy if given within 9 weeks of chemotherapy.(189) Other meta-analyses have found that early radiotherapy increases survival but causes more side effects e.g. severe oesophagitis.(190, 191)

Prophylactic cranial irradiation

Our findings align with a systematic review by *Aupérin et al* that demonstrated prolonged overall survival with PCI for LD-SCLC.(192) Conversely, we found that PCI did not augment survival for ED-SCLC, similar to a finding by *Takahashi et al*.(193) In their study people with ED-SCLC who had responded to chemotherapy were randomized to either; surveillance magnetic resonance imaging of the brain (3-monthly for 12 months then scans at 18 and 24 months after enrolment) or PCI. The study was terminated early as it was clear that PCI was not beneficial to survival. This finding, in

conjunction with our study, provides strong evidence that, for the most part, PCI in ED-SCLC has a limited role.

Relevance to practice and guidelines

The European Society of Medical Oncology SCLC clinical practice guideline was published in 2013 and therefore new data are not incorporated. However, Table 4 compares our conclusions with these recommendations and generally supports these. In particular, early thoracic radiotherapy and PCI for LD-SCLC and the cautious use of chemo-radiotherapy for people with worse PS. In contrast age, which is currently cited as a criterion for choosing cisplatin+etoposide, was not associated with poorer survival, especially in ED-SCLC. The European recommendations contain minimal information about appropriate patient selection and this can cause variation in chemotherapy administration, which is known to occur nationally.(194) Our study could reduce this variation as it quantifies survival so that better informed treatment decisions can be made. Similarly, it can assist with the appraisal of novel therapies as it is a comprehensive survival reference for current treatments.

On the whole, recommended treatments for SCLC have remained unchanged for years when compared to NSCLC. This has reinforced the nihilistic connotations associated with SCLC. We have shown that survival has improved over time in SCLC; a finding which can raise optimism for the future.

Future directions

An updated version of the ESMO recommendations is expected to be published within the next year and will reflect some of the newer developments in SCLC, particularly immunotherapy and PCI for ED-SCLC. In addition to immunotherapy other classes of drugs such as RNA polymerase II inhibitors have shown promising results in phase II clinical trials and may become available for patients with relapsed SCLC in the future.(195) Similarly, clinical trials, such as the ADRIATIC trial (NCT03703297) are exploring whether combination immunotherapy can improve survival following concurrent chemo-radiotherapy in LD-SCLC.

Conclusions

We have conducted the largest systematic review and meta-analysis of survival in SCLC. Our findings support ESMO recommendations, in particular, early thoracic radiotherapy and PCI for LD-SCLC with the cautious use of chemotherapy for people with worse PS. Cisplatin and carboplatin are preferred, however, we found significant disparities in their long-term survival by ethnicity. This may relate to altered drug metabolism and the differing aetiological exposures for SCLC across ethnic groups.

At present, early mortality risk is not included in the criteria for chemotherapy administration but it is a metric that can inform patient selection. Early mortality risk does not increase for the elderly and age should be cited cautiously as a selection factor. There is great optimism surrounding immunotherapy as it has the potential to revolutionise prognosis in SCLC. Importantly, our research sets a reference point for survival following current treatments to which the success of immunotherapies can be measured.

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Gavin Jones: Designed the systematic review as well as search strategy, data extraction, meta-analysis and write up of manuscript. Dr Jones is the Guarantor.

Kelly Elimian: screened manuscripts and extracted data for the meta-analysis

David Baldwin: Designed the study, assisted with writing and interpretation of findings.

Richard Hubbard: Designed the study, assisted writing and interpretation of findings

Tricia McKeever: Designed the study, assisted developing search strategy, screening, data extraction, writing and provided statistical support for meta-analysis.

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Figure legend

Figure 1: PRISMA flow diagram of the initial electronic search and screening of abstracts and manuscripts.

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