SCLC – ASCO 2009

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For years interest in developing new treatment strategies in SCLC has lagged behind the efforts addressing NSCLC. This trend could easily be followed during the ASCO 2009 meeting. Fifty-two abstracts relating to SCLC were exhibited, whereas 392 abstracts covered NSCLC research topics. None of the presentations dealing with SCLC showed successful phase III results no results were presented in the lung cancer oral presentation session. We are left with efforts in challenging the first-line standard regimen of etoposide/platinum (EP) with the irinotecan/platinum (IP) regimen as an alternative to the first-line standard regimen of etoposide/platinum oral presentation session. We are left with efforts in challenging the first-line standard regimen of etoposide/platinum (EP) with the irinotecan/platinum (IP) regimen as an alternative treatment choice with comparable results but different toxicity. Randomised phase II results with amrubicin seem to support the use of second-line treatment in an otherwise chemoresistant and desperate disease. In various trials most of the investigated new targeting agents did not lead to a reproducible improvement in the outcome of SCLC patients. After ASCO 2009 it seems that progress in the treatment of SCLC requires not only a tailored medical approach, which is difficult to achieve, but also changes in therapeutic strategies in radiotherapy and surgery for LD-SCLC.

Keywords: SCLC, chemotherapy, irinotecan, amrubicin, targeted

Introduction

Numerous successful phase III trials including various agents have led to the significant improvement of patient survival in NSCLC within the last 10 years; however, not a single phase III trial showed impact on survival in SCLC in the same time period.

Although the incidence of SCLC decreases further and accounts now for 13% of all lung cancer patients, there is no doubt that there is an urgent need to improve treatment outcome in this disease [1]. As chemotherapy is the mainstay of therapy in SCLC, efforts to improve this treatment strategy by means of new chemotherapeutic agents are still warranted despite growing interest in targeted therapies. The most promising agent to be combined with platinum in the first-line setting as an alternative to etoposide proved to be irinotecan. Several phase II trials presented at this year’s ASCO showed results that not only support the use of amrubicin in second-line therapy but also may help to settle its role as an alternative treatment to topotecan.

Irinotecan (I) combination in ED-SCLC 1st line

The recently published SWOG S0124 randomised phase III trial comparing the standard regimen etoposide plus cisplatin (EP) with irinotecan plus cisplatin (IP) and the NA/Australian trial using a similar – not identical – IP regimen in Caucasian population showed no improvement in OS [2, 3]. The results of these two trials were contradictory to the results of the preceding Japanese JCOG 9511 published in 2002, which showed superior OS in ED-SCLC in favour of the IP regimen [4]. The toxicity profile of the two regimens is different with EP causing more frequent G3/4 myelosuppression and IP causing more diarrhoea. In the light of these results the debate whether IP should replace EP in the first-line setting continues even though this year’s ASCO meeting added three presentations dealing with irinotecan.

Lara and co-workers analysed the pivotal JCOG 9511 and the SWOG S0124 trials using patient-level data to explore potential differences in patient characteristics that might explain the divergent results [5]. Although both protocols used identical treatment regimens, they found relevant differences in patient demographics and significant differences in toxicity and efficacy. Consequently the authors argued that these results are relevant in the era of globalisation of clinical trials. It is warranted to consider different patient characteristics of various populations and pharmacogenomic correlates where ethnic differences in drug disposition are expected.

A meta-analysis using OS as primary outcome measure addressed differences in outcome between IP and EP and was presented by Sasse et al. [6]. Four studies \((n=1,365)\) out of six had sufficient data for OS and were included in the analysis. The test for heterogeneity was acceptable only when a trial with exclusively Japanese population was excluded. For the remaining Western population the meta-analysis revealed a significant OS benefit of IP over EP with a HR of 0.86 (95% CI = 0.76–0.97, \(p=0.01\)) favouring IP. The HR for PFS was 0.96 (95% CI = 0.85–1.09, \(p=0.54\)) and the RRs were 60% for IP and 49% for EP (\(p<0.0001\)) in this analysis. As already mentioned above, the safety profiles were different in the two treatment...
arms with diarrhoea occurring more frequently with IP. This should be considered when using the IP regimen as an alternative regimen to EP.

The only phase III trial results in SCLC patients were presented by the German AIO group this year [7]. In this trial patients were randomly assigned to receive carboplatin AUC 5 mg·min/ml either in combination with 50 mg/m² of irinotecan (day 1, 8, 15) q3wks or etoposide 140 mg/m² (day 1–3) q3wks. Primary endpoint of this study was PFS. In 216 patients randomised, PFS was six months in both arms. No significant differences were observed with respect to secondary endpoints OS and RRs. Significant differences in toxicity were seen as expected from previous trials. G3/4 diarrhoea was manageable and occurred in 15% of patients treated with IP and 6% of patients treated with EP. Myelosuppression including G3/4 thrombocytopenia and neutropenia was more frequent in the EP arm although the rates of febrile neutropenia were the same. The authors concluded that both regimens proved to be equivalently effective in this setting.

Amrubicin (AMR) phase II results in ED-SCLC 2nd line

Amrubicin is a third-generation synthetic anthracycline agent with a favourable toxicity profile. AMR proved to be effective in SCLC in various trials, which led to approval in Japan for the treatment of this disease although the results of phase III trials are still pending [8].

Because AMR showed no relevant cardiotoxicity in Japanese population, Spigel et al. analysed patients treated with AMR in 2 phase II trials to determine if AMR treatment is associated with an increased incidence of cardiomyopathy [9]. To evaluate the risk of cardiomyopathy LVEF was measured by echocardiography or MUGA-scan. One hundred and twelve patients were treated with a median of 5–6 cycles and the results revealed only minimal changes in LVEF from baseline and were similar across cumulative dosing groups. The authors concluded that AMR for second-line treatment of SCLC is safe and does not appear to cause anthracycline-related cardiomyopathy. In contrast to these positive findings concerning cardiotoxicity, another important toxicity not previously described was observed by Yoh et al. in a retrospective analysis [10]. They delineated a remarkable association between the incidence of acute interstitial lung disease and amrubicin treatment in Japanese patients indicating the need for awareness of the treating physicians as long as phase III trials are still pending.

Jotte et al. presented a randomised phase II study enrolling seventy-six patients of a Western population with ED-SCLC sensitive to 1st line platinum-based chemotherapy [11]. Primary endpoint of the study was ORR for the patients receiving AMR 40 mg/m²/d (d 1–3) versus patients receiving topotecan 1.5 mg/m²/d (d 1–5) q3wks. The primary endpoint was met: AMR significantly improved response rates vs. topotecan with ORR 44% vs. 12% (p = 0.005) favouring AMR. OS and PFS were numerically higher in patients treated with AMR compared to topotecan. Myelosuppression was comparable in both arms but led to serious AEs more often in the AMR group. Although LVEF was stable with cumulative AMR dosing >1000 mg/m², the authors stated that the long-term effects are unknown.

Ettinger et al. displayed an update of a phase II trial to investigate efficacy and safety of single-agent amrubicin – first presented at last year’s ASCO – enrolling 75 Western patients with ED-SCLC refractory to prior 1st line platinum-based chemotherapy [12]. The primary endpoint of the study (point estimate: ORR ≥18%) was met with an ORR of 21% (95% CI = 13.6–31.9%). Median OS was 6.0 mos and PFS was 3.2 mos. The most common toxicity was myelosuppression as shown in other trials. AMR shows promising efficacy with an acceptable safety profile in this group of patients and warrants further study as pointed out by Ettinger in the light of these results.

Targeted agents and prognostic factors

None of the agents tested in phase I or phase II trials presented at this year’s ASCO revealed results indicating importance in the treatment of SCLC. This includes the TKI RAD001 [13], the oral 5FU-derivate S1 [14], the Bcl2 inhibitors AT-101 [15] and obatoclax [16], and the Plk1 inhibitor BI 2536 [17]. The most relevant prognostic factors displayed – if any – seem to be c-kit [18], IGFR-1 [19] and MET activation [20] but not I. ERCC1 [21]. Topo-II levels may be a potential predictor of response in the treatment of amrubicin [22].

Take-home-message

Platinum-containing regimens combined with irinotecan (IP) prove to be an equivalently effective treatment alternative to combinations with etoposide (EP) considering different toxicity profiles. Amrubicin (AMR) shows promising efficacy in phase II with an acceptable safety profile in the 2nd line treatment of SCLC.

Conflict of interest

The author declares that there is no conflict of interest.

References