short review

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Current trends in small cell lung cancer management—ASCO 2019 update

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Summary During the last 30 years the developments in small cell lung cancer (SCLC) have been extremely scarce. Concurrent chemo-radiation associated with prophylactic cranial irradiation in case of complete clinical remission is standard in limited disease. In extensive disease, platinum/etoposide and topotecan remain the standard systemic approaches in the first- and second-line setting, respectively. The only notable improvement was communicated in the IMpower133 trial, by the addition of atezolizumab to the platinum/etoposide chemotherapy backbone. Against this background, the current article aims to review the most important abstracts presented at ASCO 2019 along with their potential impact for current clinical practice.

Keywords SCLC · Management · ASCO · 2019

Take home message

In extensive disease, apart from a modest 2 month improvement in OS upon addition of atezolizumab in first line (2018), we remain attached to the standard of the last 30 years with etoposide platinum in the first-line setting and topotecan in the second-line setting.

Most oncologists are aware that during the last 30 years developments in small cell lung cancer (SCLC) have been extremely scarce. Paradoxically, in this disease with extremely high propensity for metastatic spread, improvements in overall survival were due to various radiation therapy protocols [1, 2]. Since its introduction in 1985, etoposide/platinum remains the standard chemotherapy regimen for both limited and extensive disease [3, 4]. In 2018 a small but statistically significant improvement in the overall survival time (OS) was reported in the IMpower133 trial, with the addition of atezolizumab to this standard chemotherapy backbone [5]. Despite a substantial unmet need in the first-line setting, the most important abstracts at ASCO 2019 focused on second-line alternatives. Since 1997, topotecan has been the standard of care in the second-line setting for both sensitive and refractory disease, with overall response rates (ORR) in the range of 20%, median progression-free (PFS) and OS time in the range of 3 and 6 months, respectively [6–8]. Furthermore, amrubicin and nivolumab did not provide a survival advantage over topotecan in randomized trials [8, 9].

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Lurbinectedin—a new chemotherapy drug

Lurbinectedin is a natural marine-based tetrahydroisoquinoline antitumor agent that inhibits activated transcription and induces DNA double-strand breaks, leading to apoptosis. A multicenter phase II basket trial assessed the efficacy and safety of lurbinectedin in several cancer types, including SCLC [10]. In the SCLC cohort, 105 patients with ECOG PS 0–2 who had received one prior chemotherapy line were treated. The ORR was 35%, with 21% and 47% ORR for resistant and sensitive disease, respectively. Disease control was noted in 65% of patients, median duration of response 5.3 months, and median OS 10.8 months (5.1 months for resistant and 15.2 months for the sensitive disease, respectively). As the target of ≥30% was set initially for the ORR, these results are considered promising to qualify the new drug as being clinically active. At a glance however, the results do not seem to be substantially better with lurbinectedin

compared historically with topotecan. Except for the ORR (35% vs 23%), the median PFS (3.9 vs 3.5 months) and the OS (9.3 vs 7.8 months) look pretty similar [8, 10]. Moreover, some limitations of the lurbinectedin study should be taken into consideration: a single arm phase II study, immaturity of the OS data, exclusion of patients with CNS metastases. Despite the trial drawbacks, lurbinectedin was granted orphan drug designation for SCLC by the FDA. No randomized phase III trial exploring the activity of single agent lurbinectedin is anticipated. A global randomized phase III study (ATLANTIS) comparing combination lurbinectedin and doxorubicin to either topotecan or CAV just completed enrollment, and the results are pending (NCT02566993).

Trilaciclib—attempt to decrease chemotherapy toxicity

One of the key molecular alteration in SCLC is the loss of the RB gene [11]. Trilaciclib is a selective CKD4/6 inhibitor which is predicted to arrest the hematopoietic cells in G1. As the cancer cells cycle escape the RB gene regulation administration of trilaciclib is expected to allow these cells to continue division, while arresting the normal hematopoietic stem cells. By giving trilaciclib concurrently with topotecan, a decrease in the hematologic toxicity with improved chemotherapy dose intensity is anticipated. A multicenter phase II study, including previously treated patients with extensive disease small cell lung cancer (ED-SCLC) was presented [12]. Ninety-one patients were randomized to trilaciclib ($240\,mg/m^2$) + $0.75\,mg/m^2$ topotecan, trilaciclib ($240\,mg/m^2$) + $1.5\,mg/m^2$ topotecan, or placebo + $1.5\,mg/m^2$ topotecan IV on days 1–5 of 21-day cycles. The addition of trilaciclib significantly reduced the occurrence (40.6% trilaciclib vs 75.6% placebo, $p=0.016$) and duration (2 days trilaciclib vs 8 days placebo, $p=<0.0001$) of severe neutropenia in cycle 1. In addition a trend towards less grade 3/4 anemia and fewer RBC transfusions, as well as grade 3/4 thrombocytopenia and platelet transfusions was noted. Unfortunately there was no statistical analysis to properly assess these differences. However, the median duration of drug exposure (67 vs 77 days) and median number of cycles completed (3 vs 3) were pretty similar. Moreover similar PFS (HR = 0.87, $p=0.623$) and OS (HR = 1.34, $p=0.467$) between arms with and without trilaciclib were recorded. Of note, the authors stated that the relative dose intensity of topotecan was not available *due to the blinded design of the study and two doses of topotecan being utilized.* Similar trend in reducing the myelotoxicity by trilaciclib associated with etoposide and carboplatin was also reported in the first-line setting [13].

Immune therapy—attempt to expand the armamentarium

The synergism between immune therapy and radiation was evaluated in a small trial including SCLC patients, who received no more than 2 lines of therapy, randomized to either arm A: (tremelimumab 1500 mg/durvalumab 75 mg i.v. every 4 weeks without SBRT) or arm B: tremelimumab/durvalumab with immune sensitizing SBRT to one selected tumor site (9 Gy × 3 fractions) [14]. There were no responses with tremelimumab/durvalumab alone, and two out of seven with the addition of radiation. There was no significant difference in efficacy between arms A and B with median PFS of 2.1 vs. 3.3 months (HR: 2.44; $p=0.122$) and median OS of 2.6 vs. 5.7 months (HR: 1.50; $p=0.5068$).

Rovalpituzumab tesirine (Rova-T™) is an investigational antibody-drug conjugate targeting delta-like protein 3 (DLL3), which is expressed in more than 80% of SCLC tumors but not in normal tissue. Rova-T™ was tested in combination with nivolumab alone or with nivolumab + ipilimumab in patients progressing after ≥1 line of therapy [15]. Quite substantial toxicity was noted in both arms while the best results in the triplet combination arm (ORR = 29%, PFS = 4.1 months and OS = 7.2 months) do not seem much different compared to those recorded in studies with Rova-T alone (RR = 19%, PFS = 3.9, OS = 5.6) [16].

SUKSES—an umbrella trial exploring NGS technology

Recent progress in the genomic profiling of SCLC has demonstrated that a high proportion of SCLC harbor mutations in cell cycle-related genes and RICTOR amplification [17]. SUKSES is a phase II umbrella trial study with multiple monotherapy arms in resistant SCLC with patients who have failed prior platinum-based chemotherapy and have a known genomic profile [18]. The results of 3 out of the 7 arms of the trial were presented this year. Patients with MYC family amplification or co-alteration in CDKN2A and TP53 were allocated to AZD1775 (a Wee1 inhibitor) and patients with RICTOR amplification to AZD2014 (an mTOR inhibitor). Otherwise, patients were randomly assigned to a nonbiomarker-specific arm but treated with an investigational drug (AZD2811—an aurora kinase inhibitor). There were no responses in any arm, with a mPFS between 1.3–1.6 months suggesting that virtually all patients progressed at first evaluation. Despite the fact that the study supports the feasibility of the biomarker-driven umbrella design in ED-SCLC, it does not recommend further development of the currently tested regimens.

The clinical impact of the studies presented this year at ASCO in the field of SCLC seems fairly inconsistent. Lurbinectedin may count as another option along with topotecan and amrubicine in the second-line treatment of SCLC, but without any clear ad-

vantage. Trilaciclib may have a positive impact on chemotherapy-induced myelotoxicity, but the real clinical benefit is still uncertain. Many of the patients who received trilaciclib still did require G-CSF or transfusions, while lowering the incidence of the myelotoxic events did not translate into a better outcome. Results of the combined immune therapy with radiation or Rova-T confirm the lack of immune check point inhibitors activity in the second-line or maintenance setting [9, 19]. Some activity was recorded for nivolumab in third or further lines in the CheckMate 032 trial (response rate = 13%, mOS = 5.6 months) [20]. Anyhow, the current first-line standard including atezolizumab along with etoposide platinum makes various immune therapy attempts in second and further lines rather controversial. Rova-T did not confirm any relevant clinical activity either alone [21] or in combination with the immune therapy [15].

The use of genomic profiling to find targetable alterations is feasible in SCLC. However, the investigational agents tested in the SUKSES trial did not show any sign of activity. I am looking forward to learn about the results of other experimental arm of this trial, especially the one testing the PARP inhibitor olaparib.

One can conclude that the most important papers presented at ASCO 2019 in the field of SCLC have not had an impact on the current standard of care in either limited or extensive stage SCLC.

Conflict of interest M. Dediu served as consultant and received speaker honoraria from: Boehringer-Ingelheim, Roche, Novartis, MSD, Astra-Zeneca, Bristol-Myers Squibb, Ipsen, Sandoz, Pfizer, Astellas, Merck.

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