Extended-Stage Small-Cell Lung Cancer

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Extended small cell lung cancer (ED-SCLC) is a very aggressive disease, characterized by rapid growth and an early tendency to relapse. In contrast to non-small cell lung cancer, no therapeutic innovation has improved survival in patients with ED-SCLC over the past 20 years. Recently, immunotherapy has shown an important role in the management of these patients, emerging as the treatment of first choice in combination with chemotherapy and completely changing the therapeutic paradigm. However, patients' selection for this strategy is still challenging due to a lack of reliable predictive biomarkers. Conversely, the immunotherapy efficacy beyond the first line is pretty disappointing and innovative chemotherapies or target agents seem to be more promising in this setting. Some of them are also under evaluation as an upfront strategy and they will probably change the treatment algorithm in the next future. This proposal provides a comprehensive overview of available treatment strategies for ED-SCLC patients, highlighting their strengths and weaknesses.

Keywords: SCLC ; immunotherapy ; metastatic ; lung cancer

1. Introduction

Small cell lung cancer (SCLC) accounts for approximately 13% of lung cancer diagnoses [1]. It is a very aggressive disease, characterized by rapid growth and an early tendency to metastasize. Extensive disease (ED–SCLC) accounts for more than 70% of new diagnoses with a 5–year survival of 2.8% and a median overall survival (OS) of about 10 months [2]. In contrast to non–small cell lung cancer, no therapeutic innovation has improved the survival in patients with ED–SCLC over the past 20 years [3].

2. Immunotherapy as Upfront Treatment for ED–SCLC

The introduction of immune checkpoint inhibitors (ICIs) in this context was motivated by the high mutational load characterizing this histological subtype. To note, some data suggest that lung cancer patients with a high mutational load are more likely to obtain a better clinical benefit from ICIs [4]. For this reason, the immune checkpoint inhibition may be an effective approach in this histology (Table 1). Moreover, the combination of these agents with chemotherapy may induce a synergistic effect between tumor antigens release and cytotoxic T lymphocytes boosting [5].

2.1. Ipilimumab

The evaluation of ICIs role in first–line setting began in 2009 with a phase II clinical trial comparing the combination of carboplatin–paclitaxel and ipilimumab (anti–cytotoxic T lymphocyte antigen–4/anti–CTLA–4) administered concomitantly or delayed at 10mg/kg every 3 weeks to chemotherapy alone [6]. Despite an improvement in the immune–related progression free survival (irPFS) with the combination (6.4 months for the delayed regimen vs 5.3 months for the chemotherapy alone, hazard ratio [HR] = 0.64, p = 0.03), the association did not show any OS benefit. Two subsequent studies (a phase II and a phase III) evaluated the addition of ipilimumab to platinum–etoposide–based chemotherapy [7][8]. Unfortunately, they were unable to demonstrate the superiority of the combination over chemotherapy alone.

2.2. Atezolizumab

Rather different results were obtained by atezolizumab (anti–programmed death ligand 1/anti–PD–L1) combined with chemotherapy. The IMPOWER133 randomized–controlled trial compared the association of atezolizumab 1200 mg every 3 weeks with carboplatin/etoposide (followed by atezolizumab maintenance up to disease progression) to chemotherapy alone [9]. In this phase I/III trial the primary endpoints were OS and PFS. The study showed, for the first time, a real benefit from the combination getting an OS (12.3 vs. 10.3 months; HR 0.70; 95% Confidence Interval [CI], 0.54–0.91; p = 0.007) and a PFS (5.2 vs. 4.3 months; HR 0.77; 95% CI, 0.54–0.91) improvement in the chemo–immunotherapy arm. In contrast, the objective response rate (ORR) similar being 60.2% (53.1–67) in the atezolizumab group and 64.4% (57.3–

71) in the control. To note, in the survival subgroup analysis, the survival benefit with the combination was not confirmed in patients with brain metastases, but the number of patients with this characteristic was too small (9%) to draw conclusions. Finally, there was no signal of over–toxicity with the chemo–immunotherapy having 56% of patients that experienced a treatment–related adverse events grade III–IV event in both groups. The most common toxicities in the experimental arm were neutropenia and anemia with 11.1% of patients stopping treatment due to adverse events (3.1% in the chemotherapy group). Immune–related adverse events (irAEs) were reported in 39.9% of patients in the atezolizumab arm and 24.5% in the placebo arm. Rash (18.7%) and hypothyroidism (12.6%) were the most commonly reported.

The PD–L1 status was not considered at inclusion and, interestingly, the mutational load was not associated with treatment response in terms of survival, any threshold considered. No clinical or biological predictive characteristic were identified [10].

Table 1. Results of phase II and III trials in first–line setting including ED–SCLC patients.

Study Phase	Exp Arm	Ctrl Arm	N	OP	ORR		PFS (Months)		OS (Months)		Treatment–Related Adverse Events Grade III/ IV	
					Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
CASPIAN (III)	PE + durvalumab	PE	573	OS	68%	58%	5.1	5.4	13	10.3	46%	52%
IMPOWER 133 (I/III)	PE + atezolizumab	CE	403	PFS/OS	60.2%	64.4%	5.2	4.3	12.3	10.3	56.6%	56.1%
NCT03382561 (II)	PE + nivolumab	PE	160	PFS	52.2%	47.7%	5.5	4.6	11.3	8.5	77%	62%
KEYNOTE–604 (III)	PE + pembrolizumab	PE	445	PFS/OS	71%	62%	4.5	4.3	10.8	9.7	63.7%	61%
REACTION (II)	PE + pembrolizumab	PE	125	PFS	67%	56%	4.7	5.4	12.3	10.4	NR	NR
NCT00527735 (II)	CP + concurrent ipilimumab	CP	130	irPFS	43%	53%	5.7	5.3	9.1	9.9	41%	37%
	CP and CP + phased ipilimumab				71%		6.4		12.9		39%	
NCT01331525 (II)	PE + ipilimumab	NP	42	PFS	72%	NP	6.9	NP	17	NP	69%	NP
NCT01450761 (III)	PE + ipilimumab	PE	954	OS	62%	62%	4.6	4.4	11	10.9	48%	44%
ALTER 0302 (II)	PE + anlotinib	NP	27	PFS/ORR	77.7%	NP	9.6	NP	NR	NP	NR	NP

NCT00660504 (III)	P + amrubicin	PE	300	OS		69.8%	57.3%	6.8	5.7	11.8	10.3	NR	NR
NCT02289690 (II)	PE + veliparib	NP	128	PFS		71.9%	65.6%	6.1	5.5	10.3	8.9	NR	NR

Exp: experimental; Ctrl: control; PE: Primary endpoint; ORR: overall response rate; PFS: progression free survival; OS: overall survival; PE: platinum–etoposide; CE: carboplatin–etoposide; NP: not planned; P: placebo; CT: chemotherapy; NR: not reported.

2.3. Durvalumab

Recently, the CASPIAN trial provided interesting results about another chemo–immunotherapy association [11]. This was a three–arm randomized, open–label, phase III trial with either standard platinum–based chemotherapy (carboplatin or cisplatin) and etoposide, or the same chemotherapy combined with durvalumab (anti–PD–L1) 1500 mg every 3 weeks or durvalumab plus tremelimumab (anti–CTLA4) 75 mg every 3 weeks. In the immunotherapy arms, maintenance with durvalumab was performed until disease progression or toxicity. The study achieved its primary endpoint (OS) in the experimental arm associating durvalumab and chemotherapy showing 13 months of OS versus 10.3 months (HR 0.73; 95% CI, 0.591–0.909; *p*= 0.0047) with the chemotherapy alone. In terms of PFS, unlike the IMPOWER133 trial, no difference was reported (5.1 vs. 5.4 months, HR 0.78; 95% CI 0.65–0.94) but the study was not primarily designed to answer this question. The ORR was about 60% with a slight benefit in favor of the combination (68% vs. 58%). Again, there was no evidence of over–toxicity (treatment–related adverse events grade III–IV events: 46% and 52% in the experimental and control arm respectively) and the percentage of patients who had to discontinue treatment due to toxicity was 10% in both groups. The most common adverse events were anemia and neutropenia. irAEs occurred in 20% in the durvalumab arm and 3% in control arm. Hypothyroidism and hyperthyroidism (in 9% and 5% of patients respectively) were the most common.

Recently, additional results concerning the experimental arm combining platinum–etoposide with durvalumab plus tremelimumab were published [12]. Surprisingly, the anti–PD–L1/anti–CTLA 4 combination did not show any clinical benefit compared to chemotherapy alone. Moreover, no association was found between TMB and treatment response any cut–off considered [13].

HR 0.65, 95% CI, 0.46–0.91; *p* = 0.01). The secondary endpoint, the OS, was also in favor of the chemo–immunotherapy with 11.3 vs 8.5 months (HR 0.67, 95% CI, 0.46–0.98; *p* = 0.038). Response rates were lower than in other trials but they were still in favor of the combination strategy (52.2% vs. 47.7%). Treatment–related adverse events grade III–IV side effects were reported in 77% of patients treated in the experimental arm versus 62% in the control and treatment discontinuation was higher in the combination group (6.2% vs. 2%). Most common being neutropenia (47%), anemia 20%), thrombocytopenia (18%). To note, whereas the control arm seems to have under–performed in this trial compared to the literature data, the experimental arm showed a slightly lower numerical benefit compared to the CASPIAN and IMPOWER 133 studies with a worse toxicity profile.

HR 0.75, 95% CI 0.61–0.9, *p* = 0.0023) for the control arm. OS was the other co–primary endpoint but, even if a difference was achieved (10.8 vs 9.7 months in the control arm; HR 0.80; 95% CI 0.64–0.98; *p* = 0.0164) it did not met the pre–specified threshold for the statistical significance. The ORR was 71% and 62% respectively, in favor of pembrolizumab combination. Treatment–related adverse events Grade III–IV side effects were 64% in the combination group versus 61% in the platinum–etoposide group, however, discontinuation appears to be higher in the platinum–etoposide–pembrolizumab group (15% vs. 6%). irAES occurred in 24.7% and 10.3% of patients in pembrolizumab and control arms, respectively, the most common being hypothyroidism and hyperthyroidism (10.3% and 6.7% of patients, respectively). Pneumonitis occurred in 4%. Grade III–IV irAEs occurred in 7.2% of patients in the pembrolizumab arm and 1.3% in the placebo arm.

Moreover, the use of pembrolizumab–based chemo–immunotherapy in those patients achieving an objective response after 2 cycles of platinum–etoposide chemotherapy seemed to provide a more interesting benefit according to the REACTION trial [14]. In this study patients were randomized to receive pembrolizumab in combination with 4 cycles of current chemotherapy or chemotherapy alone. Maintenance with pembrolizumab up to 2 years was planned in the experimental arm. One of the co–primary endpoint (PFS) was not achieved (4.7 vs. 5.4 months, HR 0.84, 95% CI 0.65–

1.09, p = 0.194) while median OS was higher in the experimental arm being 12.3 vs. 10.4 months (HR 0.73, 95% CI 0.54–1.0, p = 0.097). Grade III–IV adverse events were observed in 43% and 36% of patients in the chemo–immunotherapy and control arm respectively.

Despite the modest benefit of chemo–immunotherapy in the IMPOWER 133 and CASPIAN trials, the limited effective options in SCLC context, has imposed the adoption of this therapeutic strategy by most national and international drug agencies. In both studies, around the 6 months, the separation of OS and PFS curves suggests the existence of specific subgroups that benefit from immunotherapy. But, the lack of reliable biomarkers does not currently allow an adequate selection of patients who can best benefit from this strategy. So, the question is no longer whether or not to give first–line chemo–immunotherapy, but rather which combination to choose. The two trials were indeed very similar in terms of target population with rather overlapping results in terms of overall survival and safety despite the different trial design. Indeed, the relevant differences in term of irAEs could be potentially explain by the different study design of the two studies being CASPIAN open–label trial and the IMPOWER 133 placebo–controlled.

Atezolizumab and durvalumab were recently approved by the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA) as upfront treatment in association with carboplatin–etoposide and platinum–etoposide respectively. The choice of platinum salt to be combined with immunotherapy appears to be relevant criteria to use, as cisplatin was only allowed within the durvalumab association. However, only 25% of patients in the CASPIAN trial received cisplatin. In addition, the number of chemotherapy courses desired may support the combination with atezolizumab (four chemotherapy courses as in the IMPOWER 133 trial) or durvalumab (six chemotherapy courses as in the CASPIAN trial).

Finally, despite the promising results of the REACTION trial, it will be necessary to evaluate the place of this association in a panorama that sees the presence of two other combinations of chemo–immunotherapy from the first course of treatment. However, it could be considered as a valid option to unfit patients that should be more likely to start with a standard chemotherapy.

It remains to be elucidated whether the observed benefit in first–line is primarily due to the maintenance therapy rather than the combination itself. In fact, in all these studies, the curves separate at six months from randomization when patients began the maintenance phase in the experimental arm. The next section is therefore focused on this issue.

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