Lung Cancer: Targets and Therapy

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REVIEW

Orphan Drugs in Development for the Treatment of Small-Cell Lung Cancer: Emerging Data on Lurbinectedin

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Abstract: Lung cancer is the leading cause of death of all cancer entities and small-cell lung cancer (SCLC) is the most malignant subtype. Despite good initial response to chemotherapy, many patients relapse early and success of second line treatment remains poor. For years, no relevant improvement of second line treatment has been achieved in the field of SCLC. Lurbinectedin, a novel RNA-polymerase II inhibitor has shown promising results in pretreated SCLC patients as single agent and in combination with other chemotherapeutic drugs leading to an orphan drug designation from the FDA. This article reviews the current data on this emerging substance and its impact on the treatment of SCLC.

Keywords: SCLC, chemotherapy, lurbinectedin, orphan drug

Introduction

Small-cell lung cancer (SCLC) accounts for about 15% to 17% of all diagnosed lung cancers. Nevertheless, due to its aggressive and rapid behavior, SCLC is the leading cause of death among all malignancies.[1] Promising progress in the field of non-small cell cancer (NSCLC) regarding targeted therapy and immunotherapy has been achieved in the last few years. However, the prognosis and therapeutic options of SCLC are still limited with a median survival of patients with extensive disease between 7 to 10 months and a 1-year survival of 20% to 40%.[2]

Despite the slight improvement of overall survival by adding checkpoint inhibitors to first line treatment,[3] and the development of other various treatment options, eg, PARP inhibitors, or cell cycle modulating agents, chemotherapy remains the backbone of SCLC therapy.[4]

Despite the good response of first line chemotherapy in SCLC, patients generally relapse early and therapeutic options in second line treatment are limited. In sensitive disease, topotecan, which is the current standard second line treatment in Europe, irinotecan and amrubicin have shown modest activity as monotherapy,[5–7] while doxorubicin and ifosfamide were revealed not to be effective in refractory relapse.[8,9] Given the disappointing results in second line therapy, new therapeutic approaches are desperately needed in the field of SCLC.

Lurbinectedin is a novel RNA-polymerase-II inhibitor showing promising results in several cancer entities. Also in SCLC, lurbinectedin has proven relevant activity leading to an orphan drug designation from the FDA in August 2018.

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In this article, we review the current literature of preclinical and clinical data on lurbinectedin in SCLC treatment.

Mechanism of Action and Preclinical Data of Lurbinectedin

Lurbinectedin (PM01183) is a derivative of ecteinascidin, a marine-derived agent that covalently binds to the DNA minor groove and thus leads to double-strand DNA breaks. Furthermore, it inhibits RNA-polymerase-II activity and promotes its specific degradation by the ubiquitin/proteasome machinery.[10,11] Lurbinectedin is a second-generation trabectedin analog with similar structure except for the C subunit, where tetrahydroisoquinoline was replaced by a tetrahydro β-carboline in lurbinectedin.[10,12] This difference may have an impact on pharmacokinetics and pharmacodynamics. It has been proposed that modification of the C-ring could enhance the direct interactions with specific factors of DNA repair.[10,13,14] It has been shown to have potent cytotoxic activity in several cell lines and murine xenograft human cancer models.[10] Furthermore, by attenuating the activity of the nucleotide excision repair (NER) mechanism, lurbinectedin was able to overcome cisplatin resistance in NER hyperactive cell lines.[12] Single lurbinectedin as well as in combination with cisplatin was effective in cisplatin-resistant ovarian tumor models.[15,16] Also, cervical cell lines and cervical cancers in xenograft mouse models were highly affected by single agent lurbinectedin.[17] Lurbinectedin was also shown to inactivate Ewing Sarcoma Oncoprotein (EWS-FLI1) by nuclear redistribution leading to promotor inactivity and decreased mRNA and protein levels.[18]

Clinical Development of Lurbinectedin

In 2014, Elez et al reported the first-in-human results of a Phase I dose finding study. They treated 31 patients with solid tumors and increasing doses of lurbinectedin. 7.0 mg as flat dose was recommended as a 1 hr infusion q3wk.[19] Neutropenia and febrile infections were the dose limiting adverse events.[19] Because of severe hematological side effects a second Phase I dose finding study was performed and recommended a flat dose of 5 mg of lurbinectedin given as 1 hr infusion on day 1 and 8 every 3 weeks.[20] A further Phase I study evaluated the recommended dose for the combination of lurbinectedin and gemcitabine (3 mg lurbinectedin and 800 mg/m2 gemcitabine given on day 1 and 8 every 3 weeks).[21]

A case study of two patients with mesothelioma reported disease stabilization in both patients for 5.5 and 6 months in second line treatment combining cisplatin and lurbinectedin.[22]

After promising preclinical results in ovarian cancer, lurbinectedin was tested in a randomized Phase II study versus topotecan in patients with platinum refractory ovarian cancer and showed a 23% response rate.[23] There are also hints of some activity of lurbinectedin in BRCA mutated breast cancers.[24]

Despite good response in gynecological tumors, a Phase I study in patients with acute myeloid leukemia and myelodysplastic syndrome did not show a sustainable effect.[25]

Lurbinectedin in SCLC

As a promising chemotherapeutic agent in several tumor types, lurbinectedin was also evaluated in SCLC. Furthermore, RNA-polymerase II is commonly hyperactivated in SCLC indicating a good point of attack.[26]

A Phase I study combining doxorubicin and lurbinectedin in 27 relapsed SCLC patients found remarkable activity in a second line setting.[27] 91.7% of patients with platinum-sensitive disease and 33.3% of patients with resistant disease did respond to the combinational therapy. The progression free survival (PFS) was 5.8 and 3.5 months respectively. In third line, 20% of patients, all with resistant disease, responded to doxorubicin and lurbinectedin with a median PFS of 1.2 months.[27] An expansion cohort with reduced dose was implemented in this study to improve safety. Patients with no more than one prior chemotherapy line and stable brain metastases were included. Doxorubicin was interrupted after 10 cycles continuing with lurbinectedin alone.

Overall confirmed ORR was 37% in resistant patients and 53% in patients with sensitive disease. Overall median PFS was 3.4 months (95% CI, 1.5–6.2), being 1.5 months (95% CI, 0.8–3.4) in resistant patients, and 5.7 months in sensitive patients. Overall median OS was 7.9 months (95% CI, 4.9–11.5), 4.9 months (95% CI, 2.3–6.7) in resistant and 11.5 months (95% CI, 6.0–16.6) in sensitive patients.[28]

Recently, the results of a Phase II basket trial investigating the safety and efficacy of lurbinectedin as a single agent in several tumor types were presented. 105 patients with SCLC were enrolled in the study. They had to have at least one prior chemotherapy session. Patients with CNS metastases were excluded from the study. The overall

Table 1 Clinical Trials Investigating Lurbinectedin in SCLC

Phase	Line of Treatment	Regime	N	RR% (95% CI)	PFS	OS	Grade 3/4 Toxicities	Ref.
I	2nd and 3rd	Doxorubicin 50mg/m^2 plus lurbinectedin 4.0mg, day 1 q3wk	27	2nd-line: 91.7% in sensitive patients 33.3% in resistant patients 3rd-line: 20% all resistant	2nd-line: 5.8 months in sensitive patients 3.5 months in resistant patients 3rd-line: 1.2 months all resistant	n.r.	Fatigue (11%) Mucositis (11%) Neutropenic infections (5%) Pneumonia (11%) Anemia (47%) Febrile neutropenia (26%) Leukopenia (79%) Thrombopenia (27%) Liver enzyme elevation (15%)	(27)
Ib	2nd	Lurbinectedin 2mg/m^2 plus doxorubicin 40mg/m^2 (max. 10 cycles)	27	Overall: 37% Sensitive: 53%	Total cohort: 3.4 (1.5–6.2) Resistant disease: 1.5 (0.8–3.4) Sensitive disease: 5.7 (n.r.)	Total cohort: 7.9 (4.9–11.5) Resistant disease: 4.9 (2.3–6.7) Sensitive disease: 11.5 (6.0–16.6)	Neutropenia (64%) Thrombopenia (7%) Febrile neutropenia (10%)	(28)
II	2nd	3.2 mg/m^2 lurbinectedin, day 1 q3wk	105	Total cohort: 35.2% (26.2–45.2) Resistant disease: 22.2% (11.2–37.1) Sensitive disease: 45.0% (32.1–58.4)	Total cohort: 3.9 (2.6–4.6) Resistant disease: 2.6 (1.3–3.9) Sensitive disease: 4.6 (3.0–6.5)	Total cohort: 9.3 (6.3–11.8) Resistant disease: 5.0 (4.1–6.3) Sensitive disease: 11.9 (9.7–16.2)	Neutropenia Anemia Febrile neutropenia ALT increase fatigue, thrombocytopenia	(29)
III ATLANTIS	2nd	Lurbinectedin plus doxorubicin vs cyclophosphamide plus doxorubicin plus vincristine vs topotecan	613	Not yet reported	Not yet reported	Not yet reported	Not yet reported	

Abbreviations: N, number of patients; RR, response rate; PFS, progression-free survival; OS, overall survival.

response rate was 35.2% (95% CI, 26.2–45.2). Median PFS was 5.3 months (95% CI, 3.5–6.4) and median OS 10.8 months (95% CI, 6.5–12.2).[29] Patients with sensitive disease had a better response and outcome than patients with resistant disease.

For comparison, the pivotal study of topotecan, the current standard in second line treatment in relapsed disease, revealed an ORR of 24.3%, a median PFS of 13.3 weeks, and a median OS of 25.0 weeks.[5] Besides, irinotecan as monotherapy in pretreated patients showed an ORR of 17.5%, a median PFS of 11.3 weeks, and a median OS of 13.3 weeks.[6] The topoisomerase II inhibitor amrubicin has also been investigated in second-line treatment. Kimura et al performed a meta-analysis of 296 SCLC patients treated with amrubicin. Even patients with refractory disease achieved an ORR of 36.8% and survival of 5.3 to 11 months.[7]

The ongoing ATLANTIS trial (NCT02566993) is a Phase III study investigating the combination of lurbinectedin and doxorubicin compared with either cyclophosphamide, doxorubicin, and vincristine (CAV) or topotecan in patients with relapsed SCLC, with a primary endpoint of OS. The trial has completed enrollment and results are expected next year. Table 1 summarizes the clinical trials investigating lurbinectedin in SCLC. Severe adverse events were relatively frequent in all lurbinectedin studies. Especially hematological side effects such as neutropenia and thrombopenia were typical events. Table 1 summarizes the grade 3 and 4 toxicities. However, the frequency of severe adverse events in patients with lurbinectedin alone is comparable with that seen in topotecan treatment.

Summary and Outlook

In this article, we reviewed the current data on lurbinectedin in the treatment of SCLC. The results of the Phase I and Phase II trials proved lurbinectedin to be a promising agent with potent antitumor activity. Especially in patients with platinum-sensitive disease, the activity of lurbinectedin seems to be notably high. This could be a subgroup of patients that in particular might benefit from lurbinectedin in second line treatment. Nevertheless, in SCLC many promising results from Phase I/II studies turned out to be negative in randomized trials. That is why the results of the randomized ATLANTIS trial are wishfully awaited. If they can confirm the earlier study results lurbinectedin will probably become a new standard in second line treatment of SCLC.

However, taking into account the increasing impact of immunotherapy, also in the field of SCLC, every novel agent will be faced with new standards of care in first and second line. Accordingly, new randomized studies are needed to evaluate the significance of lurbinectedin as single agent or in combination with chemotherapy and/or checkpoint inhibitors in the treatment of SCLC patients.

Disclosure

Prof. Dr. Rudolf M Huber reports personal fees from AstraZeneca Germany, personal fees from BMS Germany, personal fees from Bayer, personal fees from Boehringer Ingelheim Germany, personal fees from Lilly Germany, personal fees from MSD Germany, personal fees from Novartis Germany, personal fees from Pfizer Germany, personal fees from Roche Germany, and personal fees from Takeda, outside the submitted work. The authors report no other conflicts of interest in this work.

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