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Case Report

Is Intravenous and Oral Topotecan in Small-Cell Lung Cancer Truly Equal? A Case Report

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Abstract
Introduction: Treatment with topotecan is standard-of-care therapy for relapsed small-cell lung cancer (SCLC). Both oral and intravenous administrations of topotecan have been extensively researched and are found to be equally effective with less adverse events in the oral group. ***Case Presentation:*** We report a case of a patient with SCLC, who had previously received oral topotecan, with radiological stable disease with no changes in tumor or metastasis diameter size after two administrations. Subsequently, this patient received intravenous topotecan instead of oral due to supply difficulties. After one administration of intravenous topotecan, we saw significant disease regression. ***Conclusion:*** This is to our knowledge the first reported case of better response of intravenous topotecan than oral topotecan. Multiple extrinsic (e.g., food, medication) factors were investigated but could not deliver an explanation.

Introduction

Small-cell lung cancer (SCLC) has a dismal prognosis. Prognosis is slightly better in limited disease SLCC, for which the standard-of-care therapy is early concurrent chemoradiation therapy [1]. In patients with metastatic disease, backbone of therapy is

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platinum (carboplatin or cisplatin and etoposide) and recently the addition of PD-1/PD-L1 inhibitors has marginally improved overall survival [2, 3]. Extended-stage SCLC relapses in nearly all patients after first line of treatment. There are several options for second-line treatment, such as irinotecan, cyclophosphamide-doxorubicin-vincristine, lurbinectedin, and amrubicin. As for sensitive recurrent SCLC, topotecan is standard of care; however, refractory SCLC will demand other agents [4]. A phase III trial indicated that oral topotecan was associated with prolonged survival and quality-of-life benefit in relapsed SCLC [5].

Topotecan can be administered orally or intravenously. The cytotoxic mode of action of topotecan is by inhibition of topoisomerase 1. This results in damage during DNA replication and ultimately in tumor cell death [6]. Three different phase II studies have shown response rates of topotecan IV between 14% and 38% among patients [7–9].

A phase II and phase III study compared oral and IV topotecan in SCLC patients. These studies showed equal response rate for oral versus IV topotecan and less adverse events in the oral topotecan group. This offers a convenient alternative to IV topotecan therapy that is widely adopted [10, 11].

This case report shows a difference between IV topotecan and oral topotecan in disease response. It could open up discussion if all patient group benefits from oral therapy and which cofactors could influence the response.

Case Report

A 78-year-old male patient, with a history of smoking, consulted with a cough and worsening dyspnea. After further investigations, he was diagnosed with a small-cell lung carcinoma of the right lung with pleural and lymph node metastasis. Treatment with chemo- and immunotherapy was administered (carboplatin-etoposide-atezolizumab). The patient received 4 cycles of carboplatin-etoposide-atezolizumab obtaining a deep partial response after which atezolizumab maintenance was initiated. Disease evaluation after 6 weeks of atezolizumab in monotherapy already showed progressive disease.

The patient who remained in an excellent performance status received second-line treatment in the form of topotecan oral administration. Evaluation after two cycles of oral topotecan showed a stable disease without disease regression as shown in Figure 1a and b.

Initiation of the second cycle had to be postponed for 1 week due to (asymptomatic) neutropenia. Thereafter, due to supply difficulties of topotecan tablets, he received a continued intravenous treatment regimen. Disease evaluation after this switch showed significant disease regression with remarkable volume decrease of the primary tumoral mass, pleural lesions, and lymph nodes, whereas after the first 2 cycles no change was seen at all as shown in Figure 1c. We also note a better subjective tolerance to the intravenous administration. The patient received a total of 8 cycles of topotecan after which he developed disease progression again after 3 months of response (cfr. timeline; Fig. 2). Tolerance was relatively good, with little subjective side effects and mainly hematological adverse effects such as neutropenia and anemia for which growth factors and transfusions became necessary.

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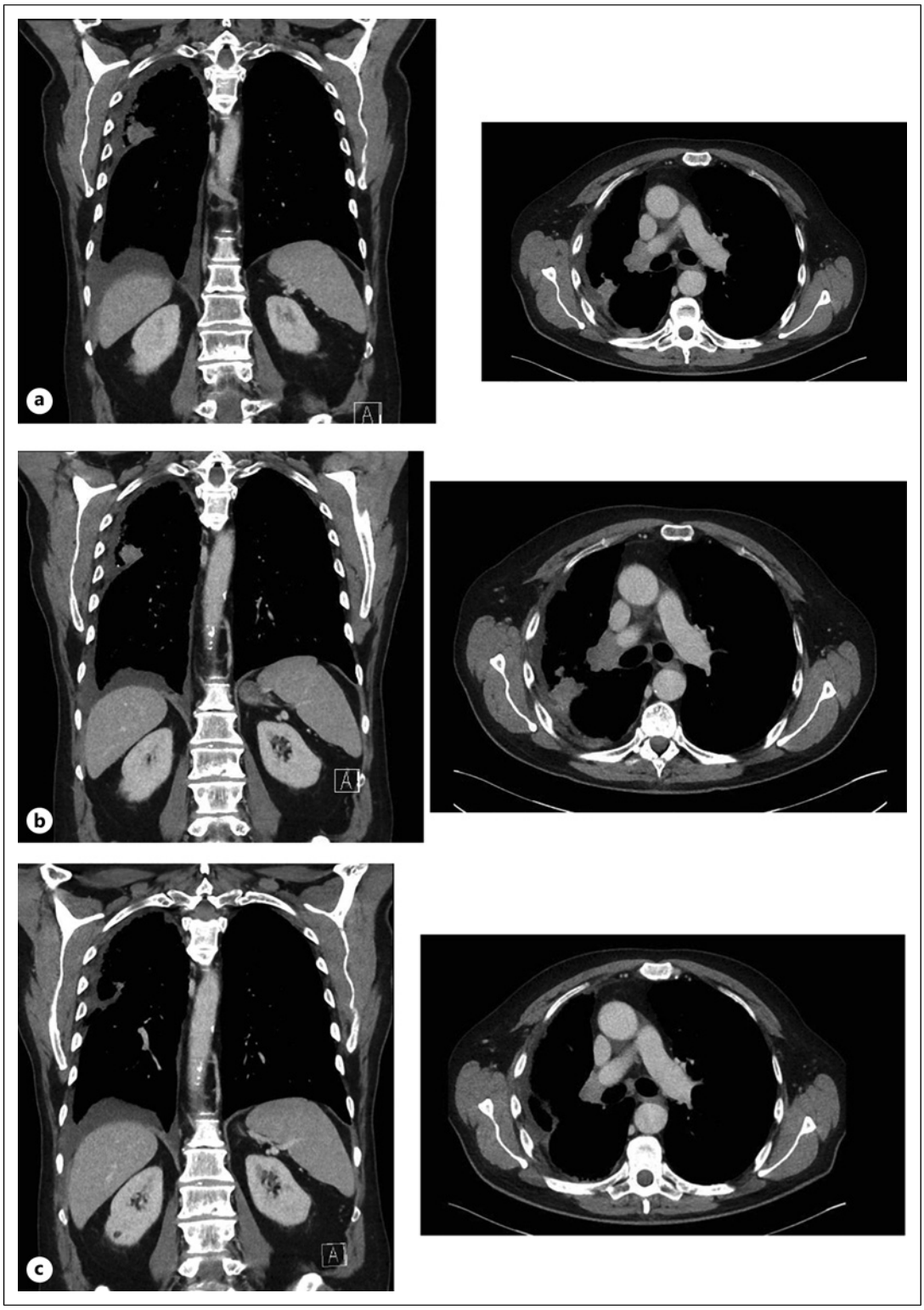

Fig. 1. a Baseline (May 25, 2023). **b** After cycle 1 and 2 PO Hycamtin (July 13, 2023). **c** After cycle 2 and 3 IV Hycamtin (July 13, 2023).

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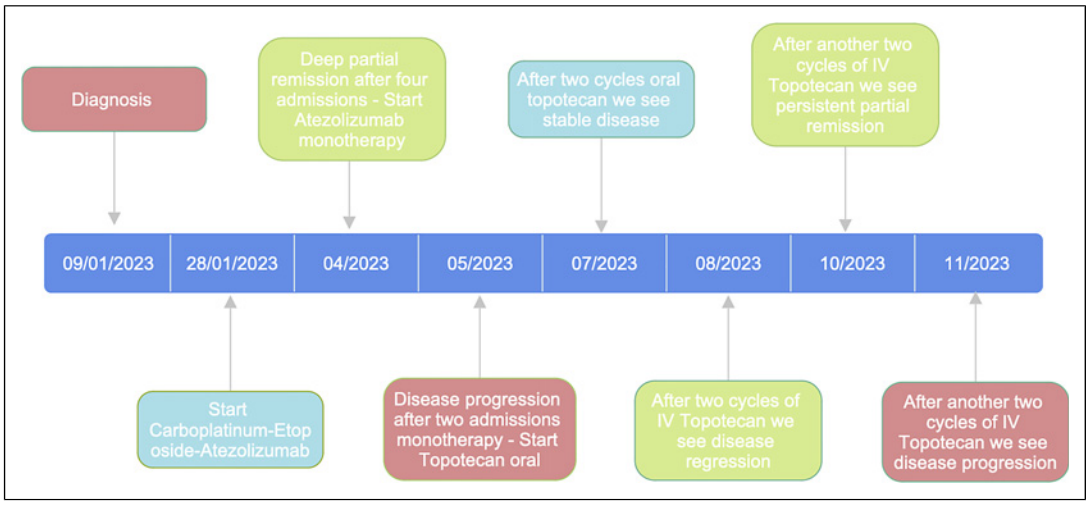

Fig. 2. Timeline.

Discussion

This case shows a remarkable disease response after switch from PO to IV topotecan. IV topotecan is considered to be similar in efficacy to oral topotecan. A phase II study showed no statistically significant differences in overall response rate and survival between oral and intravenous administrations [10]. These findings were confirmed in a phase III study comparing oral and IV topotecan in the treatment of relapsed, chemosensitive SCLC. Overall response rate was comparable between orally (18.3% [95% CI, 12.2%–24.4%]) and intravenously (21.9% [95% CI, 15.3%–28.5%]) treated patients. Difference in response rates (oral – IV) was −3.6% (95% CI, −12.6% to 5.5%). The study was not able to demonstrate noninferiority for survival of oral topotecan, because the prespecified confidence interval was not met [11].

We could not demonstrate any extrinsic influencing factors for inferior response to the oral administration in our patient. There is some evidence showing that intake of oral topotecan with a high-fat breakfast influences the absorption rate [12]. We thoroughly inquired into the dietary habits and potential use of alimentary supplements of our patient but could not withhold any abnormalities. All concomitant medications during the oral administration of topotecan were revised. Multiple drug-drug interactions are known for topotecan. Some increase metabolization of topotecan (such as but not limited to azoles, cyclosporine, macrolide, etc.), leading to reduced plasma levels; however, no such drugs could be identified in our patient [13].

In our patient, treatment with IV topotecan was well tolerated and led to a better disease response, as described above. There is little difference in cost between oral and intravenous topotecan, but we should consider the added cost of hospital or daycare patient care [14].

This case could suggest that in certain patients IV topotecan is able to induce more pronounced responses, than peroral. We should however be aware of some potential confounders. First, we note a limited delay in oral administration of the second cycle due to neutropenia. Second, full therapy compliance could not be objectively verified, but extensive drug anamnesis was performed, and the patient reported to have taken his medication as prescribed.

Personally, I think we should differentiate between geriatric patient and non-geriatric patient. We all know therapy compliance is a great issue in the elderly. Not only cognitive impairment, but also polypharmacy and dietary problems could lead impaired uptake off oral

chemotherapy. Oral topotecan persists being the standard of care, but in certain patients I think we should consider IV therapy.

New therapy options are being investigated in second-line treatment of SCLC. For example, lurbinectedin shows great overall response and has a good safety profile. It is now being investigated in a randomized phase III trial in combination with doxorubicin as second-line therapy [15]. We should also look forward to the new DLL3-targeted bispecific T-cell engager therapy with high potential in the second-line treatment of SCLC in new studies [16].

Conclusion

This to our knowledge is the first reported case of better response to IV administration of topotecan than to oral administration in a patient with an extensive stage small-cell lung carcinoma with pleural metastasis and lymph node invasion. Not only do we see radiological regression with the start of intravenous administration, but we also see better subjective tolerance in this patient. These clinically significant findings could suggest that a subgroup of patients is more suited for intravenous treatment. The CARE Checklist was completed by the authors for this case report and is included as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540861).

Statement of Ethics

This research complies with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed equally to this manuscript and approved the final manuscript: Davien Deraedt (corresponding author), Saartje Verfaillie (coauthor), Jokke Wynants (coauthor), and Kristof Cuppens (coauthor).

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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