Editorial

Is combined chemotherapy with cisplatin, etoposide and irinotecan the new standard treatment for patients with sensitive relapsed small cell lung cancer?

Alessandro Morabito

Oncologia Medica Toraco-Polmonare, IRCCS Istituto Nazionale dei Tumori, Fondazione Pascale, Napoli, Italy

Correspondence to: Alessandro Morabito, MD. Director of Thoracic Medical Oncology, National Cancer Institute, Via Mariano Semola, 80131 Naples, Italy. Email: a.morabito@istitutotumori.na.it; alessandromorabito1@virgilio.it.

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Treatment of small cell lung cancer (SCLC) remains a significant challenge for the oncologists. Attempts to improve the results of first- and second-line treatment have all failed so far and no real progress has been made in last years, emphasizing the need for novel strategies of treatment. Patients with relapsed SCLC are usually classified into different categories, according to the time elapsed from the end of previous treatment: sensitive, if tumor progression is documented at least 3 months after the completion of initial treatment, or resistant if tumor progression occurs within 3 months. In sensitive patients, the same platinum-based treatment used as first-line can be re-administered, although there are no randomized trials definitely demonstrating the efficacy of this rechallenge strategy (1). Moreover, the chance of obtaining a new response is higher in patients which had previously obtained a complete response and a long treatment free interval (2,3). In a non-randomized study in Japanese patients, the rechallenge did not demonstrate progression-free survival (PFS) or overall survival (OS) superiority compared to other regimens, but the small number of patients and the retrospective nature of the study did not allow a definitive conclusion on this topic (4). Several agents have shown modest activity in phase II trials, and to date, topotecan is the only approved drug for the second-line treatment of SCLC patients (5). In four randomized clinical studies conducted with topotecan in patients with relapsed SCLC, intravenous topotecan was compared with best supportive care (BSC), combined chemotherapy with cyclophosphamide, doxorubicin and vincristine (CAV), oral topotecan and amrubicin: topotecan improved OS and quality of life compared with BSC, while CAV and amrubicin did not show any survival benefit compared with topotecan (6-9). Although the efficacy of topotecan was low, with response rates from 7% to 24% and OS from 5.8 to 9.9 months, no regimen showed superiority over topotecan that continues to be considered as the standard second-line chemotherapy for patients with relapsed SCLC. Irinotecan showed promising activity in patients with relapsed SCLC and it was used as single agent or in combination with etoposide, with the aim to enable the synergistic effects of a topoisomerase II inhibitor (etoposide) and a topoisomerase I inhibitor (irinotecan) (10-12). The feasibility and the activity of a weekly chemotherapy regimen consisting of cisplatin plus etoposide plus irinotecan, with granulocyte colony-stimulating factor (G-CSF) support was first evaluated in a phase I trial (JCOG9507) and then in a phase II study, where this combination chemotherapy regimen showed a 78% of responses and a median OS of 11.8 months, supporting the further development of the combination (13,14).

JCOG0605 is a large, multicentre, open-label, randomized phase III trial that evaluated a combination chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for Japanese patients with sensitive relapsed SCLC (15). The study met the primary

and secondary endpoints: combination chemotherapy with cisplatin plus etoposide plus irinotecan improved OS compared with topotecan (18.2 *vs*. 12.5 months; HR: 0.67; P=0.0079). Moreover, PFS was significantly longer (5.7 *vs*. 3.6 months; HR: 0.50; P<0.0001) and the proportion of patients who achieved an objective response was significantly higher (84% *vs*. 27%; RR: 0.32; P<0.0001) in the combination chemotherapy group than in the topotecan group. Combination chemotherapy was associated with a worst toxicity profile, in terms of grade 3 or 4 anemia, febrile neutropenia and thrombocytopenia, without difference in treatment-related deaths (1 in the combination chemotherapy group and 2 in the topotecan group). Other strengths of the study are the statistical design, allowing the detection of a 33% prolongation in OS (primary objective), the large sample size (180 patients), and the balance of the subsequent regimens of chemotherapy between the two groups. Limitations of the study, as highlighted by the authors themselves, are the lack of quality of life as endpoint, considering the palliative aim of the treatment, and the chosen dose of topotecan (1.0 mg/m^2), lower than the approved dose (1.5 mg/m^2), commonly considered very toxic.

The authors concluded that this is the first time that any regimen has shown a survival benefit compared with single-agent topotecan in SCLC and that combination chemotherapy with cisplatin plus etoposide plus irinotecan could be considered the new standard second-line chemotherapy for selected patients with sensitive relapsed SCLC. We agree with the first statement, but we think that there is less data to support the second conclusion, at least in patients of Western countries. In fact, the results obtained with this irinotecan based regimen in Japanese patients can't be generalized to patients of Western countries, considering the contrasting results observed in first line with irinotecan combinations between trials conducted in Japan and in North America, probably due to the presence of inherent genetic differences that exist between North American and Japanese populations, resulting in different outcomes with the same cytotoxic agents (16-19). Moreover, if this is the first time that a regimen has shown a survival benefit compared with single-agent topotecan in relapsed SCLC, actually we don't know if this benefit is due to the addition of irinotecan to a platinum-based regimen or just to the rechallenge with a platinum-based regimen. Only a dedicated phase III study could answer this question that, to date, seems to be less crucial than in the past, in consideration of the recent development also for SCLC of new promising drugs, including immune checkpoints inhibitors or rovalpituzumab, an antibody-drug conjugate recognizing DLL3.

In conclusion, the JCOG0605 study showed that combined chemotherapy with cisplatin, etoposide and irinotecan is an effective treatment for selected Japanese patients with sensitive relapsed SCLC, but it could be also considered more generally as evidence supporting a rechallenge strategy with platinum and etoposide in this setting of patients. The results of ongoing trials with immune checkpoints inhibitors or rovalpituzumab could represent a significant advance in the treatment of patients with relapsed SCLC, radically changing the current therapeutic scenario that remains unsatisfactory.

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