Should adjuvant treatment be offered to patients with stage IB non-small cell lung cancer?

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In this issue of *eClinicalMedicine*, Ou and colleagues published the results of the CORIN (GASTO1003), phase II, randomised trial, comparing adjuvant therapy with first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), icotinib, versus clinical observation in 128 patients with surgically resected, EGFR-mutant, stage IB (7th TNM edition) non-small cell lung cancer (NSCLC) without adjuvant chemotherapy.[1] The study met its primary endpoint showing a significant increase of 3-year disease free survival (DFS), reported to be 96% in the icotinib group compared to 86% in the observation group, with a reduction in the risk of progression/death around 77% for icotinib-treated patients, confirmed also when adopting the 8th edition of the TNM staging system. The median duration of icotinib therapy was 12 months and the treatment was overall well tolerated with only 6% of grade 3–4 AEs reported in the icotinib-treated patients, including rash, diarrhoea, and pain. Despite several intrinsic limitations, including the phase II design, the small sample size, the restriction to Chinese population, and the immature overall survival (OS) data, this trial provides important evidence supporting the efficacy of post-surgical 1-year EGFR-TKI therapy in EGFR-positive patients with stage IB NSCLC who did not receive adjuvant chemotherapy.

The adjuvant treatment of stage IB NSCLC has always represented a challenging and controversial topic for medical oncologists, with subgroup analysis of historical randomised adjuvant clinical trials,[2] adopting either the 6th or the 7th edition of TNM system, showing a limited but significant OS benefit from platinum-chemotherapy for patients with stage IB tumors ≥4 cm, corresponding to stage IIA (T2b, N0) of the 8th TNM version. On this basis, the international lung cancer guidelines currently do not recommend any adjuvant chemotherapy for surgically resected patients with stage IB NSCLC, who are routinely considered as candidates to radiological follow-up.[3] Looking to the EGFR-mutant population, the majority of clinical trials testing first-generation EGFR-TKIs in the adjuvant setting (EVAN, CTONG1104, EVIDENCE, IMPACT) were limited to stage II-IIIA disease.[4] The randomised phase III ADAURA study has recently shown a 60% reduction in the risk of progression/death for stage IB patients receiving Osimertinib, confirmed also when restaging according to the 8th TNM system and excluding those (26%) treated with adjuvant chemotherapy.[5–7] Differently from ADAURA, the CORIN study reached a similar clinical benefit, by administering a first-generation EGFR-TKI icotinib, reducing treatment duration (1 year icotinib versus 3 year Osimertinib) as well as treatment-related grade 3–4 AEs (6% icotinib versus 20% Osimertinib), thus highlighting the issues of optimal treatment type, intensity, and duration in this subset of patients. Indeed stage IB disease is characterised by an improved prognosis, with a lower risk of recurrences, and 5-year survival rate reported to be around 70%, as compared to 60% of stage II and 40% of stage IIIA patients, suggesting the necessity of differential and personalised approaches. A recent explorative analysis of the ADJUVANT trial, comparing gefitinib versus platinum-chemotherapy in surgically resected, EGFR-mutant NSCLC, suggested that co-occurring genomic alterations across different genes (RB1, TP53, CDK4, NKX2-1, MYC) predict different disease prognosis as well as clinical benefit from adjuvant treatments.[8] Moreover the longitudinal monitoring of circulating tumor (ct)DNA in curative-resected, stage I-IIIA, EGFR-mutant NSCLC patients, has shown to significantly predict 3-year DFS rates, regardless of TNM staging, emerging as a reliable tool to identify high-risk stage I patients, who may benefit from adjuvant EGFR-TKI.[9]

The increasing adoption of lung cancer screening in real word practice will likely lead to a substantial increase of stage I NSCLC detection in the upcoming years,[10] making the perioperative treatment of stage I disease a major challenge for clinical and translational lung cancer research. Some open questions to be addressed are: "Should we offer or not adjuvant treatment to stage I, surgically resected patients with NSCLC? What is the efficacy of adjuvant therapy for stage I patients with detectable and undetectable ctDNA? Will there be any space for neoadjuvant immunotherapy in stage I disease?". Most of the ongoing adjuvant/neoadjuvant targeted therapy and immunotherapy clinical trials were limited to patients with stage II-III NSCLC. Thus we need a new generation of studies specifically focusing on stage I disease aiming to provide us with relevant biological and clinical information and definitively establish

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whether or not there will be a place for targeted therapies and immunotherapy in the perioperative treatment of these patients.

In the meantime, the CORIN study, in line with the results of ADAURA trial, confirmed a great efficacy and tolerability of adjuvant EGFR-TKI therapy as exclusive post-surgical treatment for EGFR-mutant NSCLC patients with stage IB disease, supporting our treatment choices in the real-word practice scenario.

Contributors

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Declaration of interests

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