

## SYMPOSIUM ARTICLE

# Current status of adjuvant chemotherapy in NSCLC

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The use of a systemic therapy in completely resected non-small cell lung cancer (NSCLC) is reasonably justified by follow-up studies after radical resection that have shown the high proportion of distant failures over local recurrences.

Earlier trials testing the role of alkylating agents and non-specific immunotherapies uniformly failed to demonstrate any survival benefit [1].

A second series of adjuvant trials, almost all of them cisplatin-based, were subsequently performed and, in a couple of studies some benefit for adjuvant chemotherapy was observed. Common findings in these studies include the overestimation of the potential benefit of adjuvant chemotherapy, in some trials an unbalance in patients' and treatment characteristics and, for most of these studies, the impossibility of reaching the planned accrual [1].

In 1995, a meta-analysis performed in different subgroups of NSCLC receiving chemotherapy, overviewed eight cisplatin-based adjuvant chemotherapy trials in 1394 patients and demonstrated a 13% reduction of the risk of death which was close to the borderline of statistical significance ( $P = 0.08$ ). On the other hand, adjuvant chemotherapy with long term alkylating agents was significantly detrimental [2].

These findings failed to impact on clinical practice not because the absolute gain was too small but because such an estimate was still imprecise, ranging from 1% detriment to a 10% benefit. In addition the heterogeneity of surgical procedures and the difference in the staging modalities strongly limited the applicability of the results of this meta-analysis.

This 5-year survival benefit of the above mentioned NSCLC meta-analysis, which was not statistically significant, generated enough enthusiasm to prompt the planning of several randomised studies, all platinum-based ( $\pm$  thoracic radiotherapy), in completely resected NSCLC stages I-II-IIIa.

More or less at the same time several Japanese studies investigated the role of UFT (a combination of tegafur and uracil at a molar ratio of 1:4) as adjuvant treatments, alone or in combination with other agents, ending in conflicting results. At the beginning of 2004, a large adjuvant phase III study which tested UFT for 2 years versus control in resected stage I adenocarcinoma of the lung was published and the results at

5 years showed a modest, but significant overall survival benefit ( $P = 0.035$ ) for UFT-treated patients that was essentially confined to T2 patients ( $P = 0.051$ ) [3].

Although a meta-analysis of six of these UFT studies became recently available [4] supporting a role for UFT as an adjuvant treatment, the absence of any advantage in disease-free survival for all UFT-treated arms, clearly contrast with the results of the recently reported positive, cisplatin-based adjuvant studies (IALT, NCIC-BR10, CALGB 8633, ANITA) where improvement in overall survival for patients receiving adjuvant chemotherapy was invariably associated with a similar or greater magnitude in disease-free survival. In addition it should be noted that UFT has been proven to be inactive in advanced disease [5].

Coming to the positive impact on 5-year survival rate of cisplatin-based, adjuvant chemotherapy as recently reported in 4 trials [6–9] the benefit ranged from 4.1% (IALT) to almost 15% (NCIC-BR 19). How we can explain such huge range of benefit, why such benefit was not uniformly observed across all stages in some studies (for instance in NCIC-BR19 the benefit was seen in stage II but not in stage IB while in IALT most of the benefit was confined to stage III) and how strong are the statistical considerations about these results (IALT and CALGB were closed before enrolling the original number of patients)?

There is a general tendency to compare cross-sectionally the benefit of adjuvant chemotherapy in NSCLC with that previously observed in other types of solid tumor (breast and colon cancers). However, specifically for NSCLC several potential confounding factors should be carefully taken into consideration. Firstly, all these adjuvant studies enrolled a selected patient population of which we do not know how much is representative of the whole population of completely resected NSCLC patients. Secondly, in many of these studies no information is available about the proportion of patients who during surgical resection underwent systematic lymph nodal dissection or mediastinal lymph node sampling. Thirdly, lung cancer patients frequently suffer from comorbidities, including chronic obstructive pulmonary disease and cardiovascular diseases that were found to affect significantly survival [10–11]. Additionally, an unbalance in the proportion of patients who potentially quit smoking after radical surgery may potentially account for survival differences [12]. Survival differences between ever smokers and never smokers have been recently documented also in another tobacco-related cancer [13].

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In conclusion although information in favour of adjuvant chemotherapy in completely resected NSCLC is available, more detailed analyses of the results of recent positive trials are needed to reasonably conclude that adjuvant chemotherapy is recommended for every patient who undergone radical surgery for early NSCLC and to exclude the potential of biases related to confounding factors.

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