Front-line doublets in advanced non-small cell lung cancer: The golden age for second line chemotherapy

A doublet chemotherapy, generally cisplatin or carboplatin-based, is the standard of care in the management of advanced non-small cell lung cancer (NSCLC) patients, defined as unresectable stage IIIB or stage IV disease [1]. Numerous trials have established the superiority of third generation cytotoxic agent combinations over old fashion regimens (2–4). In one of these studies published by Bonomi et al., the classical etoposide-cisplatin doublet (EC, etoposide 100 mg/m² days 1 to 3, plus cisplatin 75 mg/m² day 1) was compared with two different paclitaxel-cisplatin regimens (cisplatin 75 mg/m² plus paclitaxel 135 or 250 mg/m² as a 24-hour infusion) [3]. The median failure-free survival was 2.8 months for EC and 4.8 months in the paclitaxel arms, translating to a significant increase of median overall survival from 7.5 months to 9.9 months, respectively. Paclitaxel plus cisplatin was subsequently shown to be equivalent to the more convenient combination of paclitaxel and carboplatin (PC) which became the North-American reference regimen [5].

In this issue of Annals of Oncology, the phase III study reported by Belani et al. failed to detect the hypothesised 40% improvement in median survival comparing PC (carboplatin AUC = 6, paclitaxel 225 mg/m²) with EC (power of 85%, alpha of 0.05) as first line chemotherapy in 369 patients with advanced NSCLC [6]. Surprisingly, there is a trend for better median overall survival and one year survival rate in the EC arm (9.1 months and 37%) compared to the PC arm (7.7 months and 32%). The unexpected results of this trial may raise some concerns about the efficacy of the PC doublet, but also reflect a positive evolution in the medical management of advanced NSCLC.

Median time to progression was similar in EC and PC arms (3.6 and 4 months, respectively, P = 0.877), taking into account that patients in the PC arm received more cycles than in the EC arm (median number of four cycles versus three, respectively) and had less dose reductions (percentage of planned dose not reported). Patient populations in both arms were well balanced except for gender (more females in the EC arm). Performance status and prior weight loss had a significant impact on OS, without interacting with study results since patients were stratified at enrolment on these two factors. No details on histological subtypes and their predictive value were provided. This might be of importance because recent data outlined that specific tumour patterns may help in selecting patients for targeted therapy, but also for conventional chemotherapy agents [7].

There are still some concerns about the equivalent activity of cisplatin and carboplatin. Rosell et al. reported the first randomised trial comparing cisplatin and carboplatin, in combination with a 3-h paclitaxel infusion [8]. Median progression-free survival time and median survival time were significantly higher in the paclitaxel/cisplatin arm compared with the paclitaxel/carboplatin arm [4.8 months versus 3 months (P = 0.035), and 9.8 months versus 8.2 months (P = 0.019), respectively]. This result was further supported by a meta-analysis published by Hotta et al. that suggested the superiority of cisplatin plus a new agent over carboplatin plus the same new agent (hazard ratio = 1.106; 95% CI, 1.005 to 1.218; P = 0.039), although this type of study based on abstracted data should be interpreted with caution [9].

The unexpected high median overall survival of the EC arm in the present study is more likely to be explained by the extensive use of the second line chemotherapy than by the intrinsic efficacy of the doublet. Docetaxel, given at 75 mg/m², significantly increases median overall survival when given after a first line platin-based chemotherapy, compared with best supportive care (7.5 versus 4.6 months. P = 0.010; 1-year survival, 37% versus 11%, 2 test, P = 0.003) [10]. Pemetrexed, compared with docetaxel as a second line treatment, has shown similar efficacy [11] and both drugs are now approved in Europe and North America in this setting. In the present study, second line chemotherapy was more frequent in the EC arm than in the PC arm (51% and 39% of the patient respectively). Unfortunately, survival data following second line therapy are not provided. Taxanes were mostly used in the EC arm (33% versus 12% in PC arm). It should be noted that Hanna et al. reported that paclitaxel sensitivity and resistance in first-line treatment did not predict for a difference in response between pemetrexed and docetaxel in second-line treatment [11].

Quality of life, using the Functional Assessment of Cancer Therapy—Lung Scale (version 3), was significantly better between baseline and cycle 3 in the 51% of the patients assessed in the PC arm compared with the 44% of patients assessed in the EC arm. There was no statistical difference between baseline, cycle 5 and week 26 because of the decline in the number of patients, and no major difference between the toxicity profiles of both regimens. Here it should be noted that 9% of patients in the EC arm and 10% in the PC arm experienced cardiovascular adverse events, usually more reported in cisplatin-based regimens, related to necessary hyperhydration. A longer assessment would have been useful, since second line chemotherapy can lead to significant improvement in quality of life [11].

New treatment strategies seem to have eventually overcome the therapeutic limits reached with conventional chemotherapy,
even before defining a standard regimen. Adjunction of a VEGF-targeting antibody has proven to improve OS in the first line setting in patients with advanced non-squamous NSCLC [12]. Effort has now to be made in defining the best first line combination for each patient, based on their clinical, pathological and molecular prognostic factors. The present trial stressed the importance of second line treatment, moreover at a time when well tolerated therapies such as EGFR-targeted treatments, are ready to enter the current armamentarium against advanced NSCLC [13].

B. Besse¹, J. C. Soria¹ & T. Le Chevalier¹,²*
¹Institut Gustave Roussy, Villejuif, France; ²Institut National du Cancer, Paris, France (*E-mail: tle-che@igr.fr)

References