Editorial

Customizing chemotherapy in non-small cell lung cancer: the promise is still unmet

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Abstract: A combination of cytotoxic agents with cis-platin remains the cornerstone of treatment for the vast majority of patients with non-small cell lung cancer (NSCLC). Molecular analysis of the primary may lead better prognostication and eventually in more accurate therapeutic approaches. Data from retrospective analysis of randomized trials as well as large patients' series have suggested that chemotherapy may be customized upon molecular-genetic analysis of the tumor cells. The Spanish Lung Cancer Group (SLCG) in collaboration with French lung Cancer Group (FLCG) had conduct randomized, phase III, biomarkers-driven trial and supported simultaneously a randomized phase II trial in collaborating centers in China. Despite the evidence from the preclinical data and the results from the retrospective studies, the results of these trials published recently in *Annals of Oncology* were in favor of 'standard approach'. The present commentary tries to give some explanation for the disappointing results, provide potential solution for the future trials and explain why the vision of customizing treatment is still alive.

Keywords: Customized chemotherapy; predictive markers; non-small cell lung cancer (NSCLC)

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Advanced/metastatic non-small cell lung carcinoma (NSCLC) is a histologically diverse group of tumors that until recently has been treated homogeneously. Despite the fact that pathologists recognized major classes of squamous, adenocarcinoma, and large cell carcinoma, with subclasses and variants to ensure accurate diagnosis, to identify rare subtypes this had not influenced the clinical decisions' making. For several years this heterogeneous group of diseases was treated as one entity with combinations of "third generation" cytotoxic agents, such as taxanes, vinorelbine and gemcitabine with cis-platin, giving as result, in phase III clinical trials, a median survival time to 8-11 months.

This has changed radically during the last decay. The molecular age in lung cancer diagnostics and targeted therapeutics is driving the movement towards personalized medicine. Molecular classification has led to insights into tumor pathogenesis, prognostication and therapeutics. The genetic analysis of adequate tumor biopsy with sufficient amount of tumoral cell for detailed pathology review and subsequent molecular analysis became crucial for treatment decisions. In fact, today is required patients'-specific information into four categories: (I) histologic classification; (II) pathologic staging; (III) prognostic markers of survival; and (IV) predictive markers of therapeutic response. But only in a relative small percentage of patients with NSCLC this information is driving treatment decision. In the subset of patients with activating mutation in *EGFR* or *BRAF* or *ROS1* genes or EML4-ALK translocation targeted therapies have revolutionized the field, providing results that have never seen before with the use of chemotherapy. Despite that, for the vast majority of patients with NSCLC cytotoxic chemotherapy remains the mainstay of treatment.

There is growing evidence that customization of chemotherapy could be based on genetic/molecular analysis of tumoral cells. Several retrospective studies have shown that expression profile of specific genes implicated in mechanism of action and/or metabolism of the chemotherapeutic drugs may be used as predictive

factor for response to chemotherapeutic agents. But all these findings were never validated in prospective studies and today could be used only as hypothesis generating data for future investigations. In such an effort the Spanish Lung Cancer Group (SLCG) in cooperation with French Lung Cancer Group (FLCG) conducted a randomized biomarkers-driven trial, in which the patients have been randomized to "standard chemotherapy" with docetaxel and cis-platin or chemotherapy customized on the expression of *BRCA1* and *RAP80* expression (1). Simultaneously the SLCG support a similar phase II trial in China in order to compare the results in Asian population. First of all the investigators of the trial should be congratulated for their enormous effort to conduct such a type of study. It should be noticed that the trial was conducted in 86 centers in six different countries without any type of support for the pharmacy. Despite the strong preclinical rational and the results of retrospective analyses (2,3), the results of study were a strong disappointment. The randomized phase III trial not only failed to show any advantage from the pharmacogenetic approach but patient randomized to the standard arm experienced significantly longer median overall survival (mOS) in comparison with those whose received customized treatment (12.66 *vs*. 8.52 months respectively; P=0.006; HR, 1.56) and especially with those treated with docetaxel single agent chemotherapy in the experimental arm (adjusted HR, 2.54; 95% CI, 1.49-4.34; P=0.001). In addition, in the Chinese randomized phase trial, mOS was 10.82 months (95% CI, 2.32-19.33) in the control arm and 11.74 months (95% CI, 8.06-15.43) in the experimental arm (P=0.94; adjusted HR, 0.99).

Several reasons may have contributed to these negative results. First the feasibility of the studied approach appears to be quite low. Molecular analysis was performed in less than 60% of eligible patients in both studies. This factor may add significant bias in a biomarker-driven study and may influence the final results. On the other hand the low percentage of successfully analyzed samples emphasizes the lack of appropriate tissue samples at the time of diagnosis. In the context of personalized medicine, appropriate tumoral biopsy it is absolutely mandatory for the diagnosis and the molecular classification of the tumor.

Furthermore, the study was based on the mRNA expression of two genes using qRT-PCR after micro-dissection. Although the micro-dissection procedure could increase the specificity of the methodology several issues should be taking into account, such as: (I) modification of RNA expression due to hypoxia and cellular stress during the sampling procedure; (II) altered RNA expression during the fixation procedure; (III) post-translational modifications of mRNA in cancer cells; (IV) differential genes expression of a given gene in different subpopulations of tumor; and (V) alterations in gene expression profile after exposure to chemotherapeutic agents. These alterations will be probable better studied in circulating markers like circulating tumoral cells (CTCs), micro-RNA profiling in peripheral blood, tumoral DNA in blood, exosomes etc. Furthermore, the isolation and genetic-molecular characterization of CTCs may allow, in the near future, the non-invasive genotyping of CTCs and, thus, the continuous monitoring of the disease leading in specific tailored therapeutic decisions during the treatment (4).

Another factor that may influence the results is that expression profiling may be different across different histologic types, smoking habits, gender and mutation profiling of the tumor. For example, in our experience BRCA1 mRNA expression is significantly higher in squamous cell carcinomas of the lung in comparison with the non/squamous tumors and therefore we used different cut-off values in analysis of the results (5). The same may be the case with the smoking status or even more for example with the epidermal growth factor receptor (EGFR) mutated tumors.

Despite the negative results the trials reported by Moran *et al*., and as the author state is a paradigm of international academic collaboration in clinical and translation research. In a period that we phase the domination of industry-driven clinical research over the independent academic one, we should collaborate with our effort in order to perform meaningful clinical research. Clinical research can help the oncologist around the world in their daily clinical practice.

Finally, given the diversity of genetic aberrations underlying lung carcinogenesis, and the complexity of signaling networks governing the cellular phenotype, it would be unrealistic for single biomarker signatures to effectively define the disease profile for all NSCLC patients. Therefore, research interest should focus on the development and validation of clinically-oriented, multivariate predictive models, using "online monitoring" with re-biopsies programs or even better circulating markers, advance statistics analysis with the use of adaptive design methods, large clinical databases, guidelines and adherence to them. Most of all, it is required commitment, collaboration of clinicians, basic researchers and statisticians, but also well-informed and actively participating patients. Following this way, and despite the negative trials, we

should be optimist that with coordinating efforts we can bring the vision of customizing chemotherapy into reality.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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