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Hot Topic

The impact of personalized medicine on survival: Comparisons of results in metastatic breast, colorectal and non-small-cell lung cancers

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ABSTRACT

Breast, colorectal and lung cancers represent the three most incident forms of cancer worldwide. Among these three "big killers", lung cancer is considered the one with the worst prognosis due to its high mortality even in early stages. Due to their more favorable prognosis, breast and colorectal cancers might appear to have benefited from major advances. Most oncologists who are faced with metastatic non-small cell lung cancer (NSCLC) find the reported results very frustrating when compared with those for metastatic breast (MBC) and colorectal cancers (MCRC).

The aim of this analysis was to quantify and compare the relative magnitude of overall survival (OS) improvements in the first-line approaches in metastatic NSCLC, MBC and MCRC through the analysis of the main landmark meta-analyses and randomized clinical trials (RCTs) of commercially available drugs. Five items were considered and analyzed for each cancer. Moreover we evaluated the real clinical impact of the results reported by each item on the entire population; for each "big killer" an overall hazard ratio (HR) was estimated: 0.88 (95%$^+$ CI: 0.72–1.07) for MBC, 0.94 (95%$^+$ CI: 0.82–1.07) for MCRC, and about 0.80 (95%$^+$ CI: 0.73–0.90) for advanced NSCLC.

We showed that, in the last decades, these three tumors had important and constant OS improvements reached step by step. The relative magnitude of OS improvement seems higher in metastatic NSCLC than MBC and MCRC.

Introduction

Breast, colorectal and lung cancers represent the three most incident forms of cancer worldwide [1,2]. This has led to them being considered as "big killers." Among these, lung cancer is considered the one with the worst prognosis due to its high mortality even in early stages. Due to their more favorable prognosis, breast and colorectal cancers might appear to have benefited from major advances [2]. The knowledge of intrinsic mechanisms of cancer growth has led to the discovery of specific pathways and potential targets to focus on and the development of corresponding drug inhibitors. This approach is being applied to improve outcome results of the three "big killers" by attempting the "personalized medicine" approach in which every single tumor might potentially benefit from a custom tailored treatment.

Unfortunately, when these cancers are diagnosed in the metastatic stage of disease the treatment has only a palliative intent. During the last decades, several strategic therapeutic attempts have been made to improve the main endpoint: the overall survival (OS).

Most oncologists who are faced with metastatic non-small cell lung cancer (NSCLC) find the reported results very frustrating when compared with those reported for metastatic breast (MBC) and colorectal cancers (MCRC). Looking to their OS, this is because we are comparing three cancers with intrinsic natural history and prognosis which differ drastically among each other. However, it is also important to evaluate the relative magnitude of the OS improvement reported for each of these three tumors through the clinical research and strategic approaches developed during the last decades.

These three "big killers" have in common the development of the first-line strategic approaches including the use of chemotherapeutics, biological agents or their combination. Some of these approaches are oncogene-driven by specific selected biomarkers. The first-line approaches that are common for these three "big killers" pass through five main therapeutic options: "old drugs", "old

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versus new drugs", "biologic drugs versus chemotherapy in biomarkers unselected patients", "biologic drugs versus chemotherapy in biomarkers selected patients", "maintenance therapy."

The aim of this analysis was to quantify and compare the relative magnitude of OS improvements of the first-line approaches in metastatic NSCLC, MBC and MCRC through the analysis of the main landmark meta-analyses and randomized clinical trials (RCTs) of commercially available drugs addressing this endpoint. For each tumor of interest, the following questions were addressed: (1) in specific subgroups of patients, what is the relative improvement derived by current therapies? (2) In the overall population, what is the relative improvement provided by each therapeutic approach?

Material and methods

Criteria for considering studies for this review

For each aforementioned question we have considered only RCTs and meta-analyses which investigated drugs registered to date and available in clinical practice as first-line therapy.

PubMed, Embase and Medline were searched for eligible articles. Literature search, restricted to the English language, was performed until January 2013. Proceedings of the main International meetings (American Society of Clinical Oncology, European Society for Medical Oncology) were searched for abstracts addressing this topic. The search strings used to retrieve studies involved the following constraints: [("metastatic/advanced" AND "colon cancer") OR ("metastatic/advanced" AND "breast cancer") OR ("metastatic/advanced" AND "NSCLC")] AND ("randomized controlled trial" OR "meta-analysis").

The hierarchy for article selection was based on the following assumptions: (1) all meta-analyses available; in case of the availability of more meta-analyses addressing the same question, the most exhaustive and recent one was chosen; in case of more meta-analyses addressing the same item but including different RCTs a new meta-analysis was performed including all the eligible RCTs considered in at least one of the meta-analyses. (2) In absence of meta-analysis, the pivotal RCTs were chosen.

Statistical methods

Overall survival (OS) was chosen as the most relevant measure of clinical benefit; the hazard ratio (HR) statistics was used to detect the improvement in the OS endpoint. For the first question the following statistical methods were applied: (1) in case of multiple available trials a random-effect model was applied; the DerSimonian and Laird method [3] was used to estimate the between-studies variance (2) RCTs, in which crossover was permitted from the control to experimental arm after the progression of the disease, were considered only if crossover-free RCTs were not available; in this case the median survival post progression time (SPP) was estimated as the difference between the median OS and the median PFS of the experimental arm; the median OS of the control arm was estimated as the sum of the median PFS of the control arm plus SPP; assuming an exponential survival distribution the HR was estimated as the ratio of the median OS of the two arms (3) in case of maintenance therapy the HR was estimated as the product of the HR of the first-line innovative therapy plus maintenance therapy versus innovative therapy without maintenance therapy (HRm) with the HR of the innovative therapy without maintenance therapy versus first-line standard therapy without maintenance therapy; it was assumed that changing the starting point from the beginning of the maintenance therapy to the beginning of the first-line therapy did not modify the estimated HRm. For the second question an exponential Survival Function $S(t)$ for the reference arm and a weighted average of exponential Survival Function $S_i(t)$, $i = 1$ to n, for the experimental arm were assumed; the weighted average was defined in the following manner: each addend $S_i(t)$ was referred to a subpopulation with a different improvement in the drug therapy; each $S_i(t)$'s weight was equal to the prevalence of the subpopulation; for each HR_i with respect to the reference arm it was considered the point and interval estimate obtained by the first question; the HR of the previous fully parametric model was estimated by the maximum-likelihood method on data generated from the computer simulation. The number of evaluations of the probabilistic model, which have been used in the computer simulation, has been defined in order to obtain the same second decimal point for the lower and upper 95% CI relative to the HR estimate. A change of the median survival time simulated from 1 to 60 months was used to assure that the estimated HR was independent from the median survival time of the reference arm. In order to convey the reliability of the estimated HR an approximate 95% confidence interval (95%$^+$ CI) was constructed using the following procedure: assuming the statistical independence between the HR_i estimate the $(0.95)^{(1/n)}$ probability (p-value°) was calculated. A 100 (p-value°) %CI_i was determined for each subpopulation; the lower and upper confidence limit for each subpopulation were introduced in the previous statistical model in order to estimate respectively the lower and upper 95%$^+$ CI of the HR; 95%$^+$ CI could be considered an approximate and enlarged confidence interval because if $n = 1$ the 95%$^+$ CI is equal to a proper 95% confidence interval otherwise the HR will be in the interval calculated in this way by repetition in at least 95% of the cases.

Meta-analyses were performed and forest plots were created using Review Manager (RevMan) [Computer program] Version 5.2 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012. Statistical computing was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Our literature search yielded a total of 12,123 potentially relevant articles for MBC, 7621 for MCRC and 10,577 for NSCLC. A total of 12,102 for MBC, 7594 for MCRC and 10,554 for NSCLC were excluded as not relevant, not RCT, not first-line treatment, no appropriate outcome data, same data or multiple publications. Twenty-one articles (4 meta-analyses and 17 RCTs) for MBC, 27 papers (6 meta-analyses and 21 RCTs) for MCRC, and 23 articles for NSCLC (6 meta-analyses and 17 RCTs) were included in the analysis (Fig. 1).

Metastatic breast cancer

Anthracyclines versus no-anthracyclines containing regimens

Two recent systemic reviews were considered for this question [4,5] from which only RCTs addressing this issue were selected. Five RCTs [6–10], for a total of 281 patients (156 in anthracyclines and 125 in non-anthracyclines group), were considered eligible and a new meta-analysis was performed showing an overall HR of 0.76 (95% CI: 0.57–1.03) with all heterogeneity explained by random error (Fig. 2, Panel B).

Taxanes versus anthracyclines containing regimens

The most recent and complete meta-analysis addressing this issue was evaluated for this question [11]. Nine RCTs [12–20] comparing either anthracycline–taxane combination regimens versus anthracycline-based regimens, or single-agent anthracycline versus single-agent taxane regimens for the first-line treatment of MBC were considered eligible for a total of 3365 patients (1688