Année de publication : 2015

Paoletti X., Asselain B., Kamal M., Servant N., Huppé P., Bieche I., Le Tourneau C. (2015 Jan 1)

Design and statistical principles of the SHIVA trial.

Chinese clinical oncology : 4 : 32 : DOI : 10.3978/j.issn.2304-3865.2015.02.02

Résumé

Most molecularly targeted agents (MTAs) are expected to work in subgroups of cancer patients characterized by the presence of molecular alterations in the tumor cells. However, clinical development is generally carried out according to tumor type. The SHIVA randomized trial on the contrary has been set up to investigate which of tumor biology or tumor location and histology is the most important to select treatment in patients with cancer refractory to standard of care. Statistical principles, specificities, strengths and limitations of this trial that evaluates an omic-based algorithm to select the targeted agent are reviewed. In particular, the need for a randomized trial where the various steps to build the algorithm are explicitly described and standardized is emphasized. The impact of an algorithm that would be partly misspecified (i.e., that would lead to correct treatment selection for some tumor molecular profile but not for all) is quantified.

Torres-Roca J.F., Fulp W.J., Caudell J.J., Servant N., Bollet M.A., van de Vijver M., Naghavi A.O., Harris E.E., Eschrich S.A. (2015 Jan 1)

Integration of a Radiosensitivity Molecular Signature Into the Assessment of Local Recurrence Risk in Breast Cancer.

International journal of radiation oncology, biology, physics : 93 : 631-638 : DOI : 10.1016/j.ijrobp.2015.06.021

Résumé

Recently, we developed radiosensitivity (RSI), a clinically validated molecular signature that estimates tumor radiosensitivity. In the present study, we tested whether integrating RSI with the molecular subtype refines the classification of local recurrence (LR) risk in breast cancer. RSI and molecular subtype were evaluated in 343 patients treated with breast-conserving therapy that included whole-breast radiation therapy with or without a tumor bed boost (dose range 45-72 Gy). The follow-up period for patients without recurrence was 10 years. The clinical endpoint was LR-free survival. Although RSI did not uniformly predict for LR across the entire cohort, combining RSI and the molecular subtype identified a subpopulation with an increased risk of LR: triple negative (TN) and radioresistant (reference TN-radioresistant, hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.15-0.92, P=.02). TN patients who were RSI-sensitive/intermediate had LR rates similar to those of luminal (LUM) patients (HR 0.86, 95% CI 0.47-1.57, P=.63). On multivariate analysis, combined RSI and molecular subtype (P=.004) and age (P=.001) were the most significant predictors of LR. In contrast, integrating RSI into the LUM subtype did not identify additional risk groups. We hypothesized that radiation dose escalation was affecting radioresistance in the LUM subtype and serving as a confounder. An increased radiation dose decreased LR only in the luminal-

resistant (LUM-R) subset (HR 0.23, 95% CI 0.05-0.98, P=.03). On multivariate analysis, the radiation dose was an independent variable only in the LUMA/B-RR subset (HR 0.025, 95% CI 0.001-0.946, P=.046), along with age (P=.008), T stage (P=.004), and chemotherapy (P=.008). The combined molecular subtype-RSI identified a novel molecular subpopulation (TN and radioresistant) with an increased risk of LR after breast-conserving therapy. We propose that the combination of RSI and molecular subtype could be useful in guiding radiation therapy-based decisions in breast cancer.

Année de publication : 2014

Le Tourneau C., Kamal M., Alt M., Verlingue L., Servois V., Sablin M.P., Servant N., Paoletti X. (2014 Jan 1)

The spectrum of clinical trials aiming at personalizing medicine.

Chinese clinical oncology : 3 : 13 : DOI : 10.3978/j.issn.2304-3865.2014.05.02

Résumé

All anticancer molecularly targeted agents on the market today have been approved with one or no companion diagnostic based on a specific genomic molecular alteration. These drugs have followed the same clinical development than chemotherapeutic agents and have been developed in selected tumor types and histologies. Now, some molecular alterations have been described across different tumor types, although with variable prevalence and functional impact. The latter raises the question of whether treatment decision should be mainly based on molecular biology, independently of tumor location and histology. This approach refers to what is commonly named personalized medicine and can today be addressed in clinical trials, since major advances in high throughput technologies allow depicting most druggable molecular alterations for an affordable cost in a timeframe that is compatible with clinical practice. Several studies have been initiated that aim at personalizing medicine in oncology. They include molecular screening programs, as well as personalized medicine trials that can be divided in two categories: (I) stratified clinical trials according to either molecular alterations or tumor types; and (II) algorithm-testing trials evaluating a treatment algorithm instead of drugs efficacy. Multiple challenges are associated with personalized medicine trials, but the main one remains our ability to predict drug efficacy based on molecular alterations. It is expected that taking into account several molecular alterations for the prediction of drug efficacy using systems biology approaches will improve patients' outcome. Bioinformatics research will be an important factor of future progression in this emerging field.

Année de publication : 2013

Dillies M.A., Rau A., Aubert J., Hennequet-Antier C., Jeanmougin M., Servant N., Keime C., Marot G., Castel D., Estelle J., Guernec G., Jagla B., Jouneau L., Laloë D., Le Gall C., Schaëffer B., Le Crom S., Guedj M., Jaffrézic F., Consortium F.S. (2013 Jan 1)

A comprehensive evaluation of normalization methods for Illumina high-throughput RNA sequencing data analysis.
Briefings in bioinformatics : 14 : 671-683 : DOI : 10.1093/bib/bbs046

Résumé

During the last 3 years, a number of approaches for the normalization of RNA sequencing data have emerged in the literature, differing both in the type of bias adjustment and in the statistical strategy adopted. However, as data continue to accumulate, there has been no clear consensus on the appropriate normalization method to be used or the impact of a chosen method on the downstream analysis. In this work, we focus on a comprehensive comparison of seven recently proposed normalization methods for the differential analysis of RNA-seq data, with an emphasis on the use of varied real and simulated datasets involving different species and experimental designs to represent data characteristics commonly observed in practice. Based on this comparison study, we propose practical recommendations on the appropriate normalization method to be used and its impact on the differential analysis of RNA-seq data.

Année de publication : 2012

Galluzzi L., Vitale I., Senovilla L., Eisenberg T., Carmona-Gutierrez D., Vacchelli E., Robert T., Ripoche H., Jägemann N., Paccard C., Servant N., Hupé P., Lazar V., Dessen P., Barillot E., Zischka H., Madeo F., Kroemer G. (2012 Jan 1)
Independent transcriptional reprogramming and apoptosis induction by cisplatin.
Cell cycle (Georgetown, Tex.) : 11 : 3472-3480

Résumé

Neither the molecular mechanisms whereby cancer cells intrinsically are or become resistant to the DNA-damaging agent cisplatin nor the signaling pathways that account for cisplatin cytotoxicity have thus far been characterized in detail. In an attempt to gain further insights into the molecular cascades elicited by cisplatin (leading to resistance or underpinning its antineoplastic properties), we comparatively investigated the ability of cisplatin, C2-ceramide and cadmium dichloride, alone or in the presence of an array of mitochondrion-protective agents, to trigger the permeabilization of purified mitochondria. In addition, we compared the transcriptional response triggered by cisplatin, C2-ceramide and cadmium dichloride in non-small cell lung carcinoma A549 cells. Finally, we assessed the capacity of cisplatin, C2-ceramide and cadmium dichloride to reduce the clonogenic potential of a battery of yeast strains lacking proteins involved in the regulation of cell death, DNA damage signaling and stress management. This multipronged experimental approach revealed that cisplatin elicits signaling pathways that are for the most part

Galluzzi L., Vitale I., Senovilla L., Olaussen K.A., Pinna G., Eisenberg T., Goubar A., Martins I.,

Michels J., Kratassiouk G., Carmona-Gutierrez D., Scoazec M., Vacchelli E., Schlemmer F., Kepp O., Shen S., Tailler M., Niso-Santano M., Morselli E., Criollo A., Adjemian S., Jemaà M., Chaba K., Pailleret C., Michaud M., Pietrocola F., Tajeddine N., de La Motte Rouge T., Araujo N., Morozova N., Robert T., Ripoche H., Commo F., Besse B., Validire P., Fouret P., Robin A., Dorvault N., Girard P., Gouy S., Pautier P., Jägemann N., Nickel A.C., Marsili S., Paccard C., Servant N., Hupé P., Behrens C., Behnam-Motlagh P., Kohno K., Cremer I., Damotte D., Alifano M., Midttun O., Ueland P.M., Lazar V., Dessen P., Zischka H., Chatelut E., Castedo M., Madeo F., Barillot E., Thomale J., Wistuba I.I., Sautès-Fridman C., Zitvogel L., Soria J.C., Harel-Bellan A., Kroemer G. (2012 Jan 1)
Prognostic impact of vitamin B6 metabolism in lung cancer.
Cell reports : 2 : 257-269 : DOI : 10.1016/j.celrep.2012.06.017

Résumé

Patients with non-small cell lung cancer (NSCLC) are routinely treated with cytotoxic agents such as cisplatin. Through a genome-wide siRNA-based screen, we identified vitamin B6 metabolism as a central regulator of cisplatin responses in vitro and in vivo. By aggravating a bioenergetic catastrophe that involves the depletion of intracellular glutathione, vitamin B6 exacerbates cisplatin-mediated DNA damage, thus sensitizing a large panel of cancer cell lines to apoptosis. Moreover, vitamin B6 sensitizes cancer cells to apoptosis induction by distinct types of physical and chemical stress, including multiple chemotherapeutics. This effect requires pyridoxal kinase (PDXK), the enzyme that generates the bioactive form of vitamin B6. In line with a general role of vitamin B6 in stress responses, low PDXK expression levels were found to be associated with poor disease outcome in two independent cohorts of patients with NSCLC. These results indicate that PDXK expression levels constitute a biomarker for risk stratification among patients with NSCLC.

Année de publication : 2011

de Cremoux P., Valet F., Gentien D., Lehmann-Che J., Scott V., Tran-Perennou C., Barbaroux C., Servant N., Vacher S., Sigal-Zafrani B., Mathieu M.C., Bertheau P., Guinebretière J.M., Asselain B., Marty M., Spyratos F. (2011 Jan 1)
Importance of pre-analytical steps for transcriptome and RT-qPCR analyses in the context of the phase II randomised multicentre trial REMAGUS02 of neoadjuvant chemotherapy in breast cancer patients.
BMC cancer : 11 : 215

Résumé

Identification of predictive markers of response to treatment is a major objective in breast cancer. A major problem in clinical sampling is the variability of RNA templates, requiring accurate management of tumour material and subsequent analyses for future translation in clinical practice. Our aim was to establish the feasibility and reliability of high throughput RNA analysis in a prospective trial. This study was conducted on RNA from initial biopsies, in

a prospective trial of neoadjuvant chemotherapy in 327 patients with inoperable breast cancer. Four independent centres included patients and samples. Human U133 GeneChips plus 2.0 arrays for transcriptome analysis and quantitative RT-qPCR of 45 target genes and 6 reference genes were analysed on total RNA. Thirty seven samples were excluded because i) they contained less than 30% malignant cells, or ii) they provided RNA Integrity Number (RIN) of poor quality. Among the 290 remaining cases, taking into account strict quality control criteria initially defined to ensure good quality of sampling, 78% and 82% samples were eligible for transcriptome and RT-qPCR analyses, respectively. For RT-qPCR, efficiency was corrected by using standard curves for each gene and each plate. It was greater than 90% for all genes. Clustering analysis highlighted relevant breast cancer phenotypes for both techniques (ER+, PR+, HER2+, triple negative). Interestingly, clustering on trancriptome data also demonstrated a

Année de publication : 2010

Galluzzi L., Morselli E., Vitale I., Kepp O., Senovilla L., Criollo A., Servant N., Paccard C., Hupé P., Robert T., Ripoche H., Lazar V., Harel-Bellan A., Dessen P., Barillot E., Kroemer G. (2010 Jan 1)
miR-181a and miR-630 regulate cisplatin-induced cancer cell death.
Cancer research : 70 : 1793-1803 : DOI : 10.1158/0008-5472.CAN-09-3112

Résumé

MicroRNAs (miRNA) are noncoding RNAs that regulate multiple cellular processes, including proliferation and apoptosis. We used microarray technology to identify miRNAs that were upregulated by non-small cell lung cancer (NSCLC) A549 cells in response to cisplatin (CDDP). The corresponding synthetic miRNA precursors (pre-miRNAs) per se were not lethal when transfected into A549 cells yet affected cell death induction by CDDP, C2-ceramide, cadmium, etoposide, and mitoxantrone in an inducer-specific fashion. Whereas synthetic miRNA inhibitors (anti-miRNAs) targeting miR-181a and miR-630 failed to modulate the response of A549 to CDDP, pre-miR-181a and pre-miR-630 enhanced and reduced CDDP-triggered cell death, respectively. Pre-miR-181a and pre-miR-630 consistently modulated mitochondrial/postmitochondrial steps of the intrinsic pathway of apoptosis, including Bax oligomerization, mitochondrial transmembrane potential dissipation, and the proteolytic maturation of caspase-9 and caspase-3. In addition, pre-miR-630 blocked early manifestations of the DNA damage response, including the phosphorylation of the ataxia-telangiectasia mutated (ATM) kinase and of two ATM substrates, histone H2AX and p53. Pharmacologic and genetic inhibition of p53 corroborated the hypothesis that pre-miR-630 (but not pre-miR-181a) blocks the upstream signaling pathways that are ignited by DNA damage and converge on p53 activation. Pre-miR-630 arrested A549 cells in the G0-G1 phase of the cell cycle, correlating with increased levels of the cell cycle inhibitor p27(Kip1) as well as with reduced proliferation rates and resulting in greatly diminished sensitivity of A549 cells to the late S-G2-M cell cycle arrest mediated by CDDP. Altogether, these results identify miR-181a and miR-630 as novel modulators of the CDDP response in NSCLC.