Baianu, J Clin Trials 2012, 2:2
DOI: 10.4172/2167-0870.1000e103

Journal of Clinical Trials
ISSN: 2167-0870

Editorial Open Access

Cancer Clinical Trials Optimization and Pharmacogenomics

I.C. Baianu*

AFC-NMR & NIR Microspectroscopy Facility, College of ACES, FSHN & NPRE Departments, University of Illinois at Urbana, USA

To optimize the survival of patients in cancer clinical trials requires that rational, pharmacogenomic strategies in cancer clinical trials are adopted which include specific molecular targeting of cancer cells that are resistant to existing cancer therapies. Such novel strategies must be based on adequate cancer genomics data [1] and on a detailed understanding/modeling of cancer cell genomes, the modifications of cancer signaling pathways and the epigenetic mechanisms involved in cancer. It can be said in general that "*all cancers arise as a result of changes that have occurred in the DNA sequence of the genomes of cancer cells*" [1]. Cancer research and clinical trials are now moving into a completely new phase in which it has become feasible to obtain the complete DNA sequences for large numbers of cancer genomes that would provide essential information on how individual cancers have developed in specific patients. Novel translational oncogenomics research [2] is thus rapidly expanding through the application of highly sensitive and specific advanced technology, novel research findings, computational tools and complex models utilized to solve both pharmaceutical and clinical problems. Multiple sample analyses from several recent clinical studies have shown that gene expression data for cancer cells can be employed to distinguish between tumor types as well as to predict outcomes. Potentially important applications of such results are individualized human cancer therapies [2-4] or, in general, '*personalized medicine*' that will have to be validated through optimally designed clinical trials in cancer [4]. Such treatments based on personalized medicines form the subject of the new field of Pharmacogenomics.

Carcinogenesis is a very complex process that involves dynamically inter-connected biomolecules in the intercellular, membrane, cytosolic, nuclear and nucleolar compartments that form numerous inter-related pathways referred to as networks [2-6]. One such family of signaling pathways contains the cell cyclins. Cyclins are often over-expressed in cancerous cells [6]. This provides a basis for the development of novel rational chemotherapies and chemoprevention of cancers. Cyclins are proteins that link several critical pro-apoptotic and other cell cycling/division components, including the tumor suppressor gene *TP53* and its product, the Thomsen-Friedenreich antigen (*T- F* antigen), *Rb, mdm2, c-Myc, p21, p27, Bax, Bad* and *Bcl-2*, which all play major roles in carcinogenesis of many cancers. Cyclin-dependent kinases (CDK), their respective cyclins, and inhibitors of CDKs (CKIs) were identified as instrumental components of the cell cycle-regulating machinery. CDKs are enzymes that phosphorylate several cellular proteins thus 'fueling' the sequential transitions through the cell division cycle. The analysis of cancer models including CDKs and signaling pathways suggests the possibility of optimizing novel clinical trials through the development of rational therapies of cancer and the possibility of re-establishing cell cycling inhibition in metastatic cancer cells without subsequent transformations that lead to drug resistance [4].

On the one hand, quite remarkable progress has been made with cancer treatments through a handful of such clinical trials targeting cancer signaling pathways over the last decade [2-4,7-22]. This is the case especially with lung cancer treatments where new classes of anti-cancer medicines were thoroughly tested [23], and the development of a few new anti-cancer drugs which involved rational pharmacology [24,25], as for example in the case of *Imatinib*. Such novel anti-cancer drugs were found to prolong cancer patient lives significantly for large numbers of lung cancer patients. However, many other drugs tested in numerous cancer clinical trials were shown not to have a significant impact on the growth of malignant tumors, and thus, did not have any positive outcomes for cancer treatments. It is therefore surprising that such unsuccessful or unremarkable compounds are currently still being tested in cancer clinical trials in several large countries. Several such controversial, cancer clinical trials in a few foreign countries may be only financially-driven, rather than being rational as advocated in this article. The critical need for optimizing clinical trials in cancer could only be satisfied by multi-disciplinary teams that can obtain both the necessary cancer genomics data and corroborate such individualized cancer genome data with carefully analyzed progress of the individualized treatments of the cancer patients involved in well-designed clinical trials.

On the other hand, in spite of the remarkable progress made in cancer chemotherapy through clinical trials with novel anti-cancer drugs, the expected `magic bullet' for a complete treatment of cancers has not yet been found, and most of the clinical trials were not optimized for the maximum possible length of survival of the largest number of cancer patients involved in such advanced stage cancer trials. The latter fact raises the important issue of designing rational strategies for clinical trials in cancer that would optimize the survival rates of the maximum possible number of patients undergoing new clinical trials in cancer. The number of new anti-cancer drugs proposed for testing in cancer clinical trials is on a fast rise, and there is, therefore, an added urgency for maximizing cancer patients' survival in such clinical trials through a rational selection of new drugs and optimal treatment strategies based on a knowledge of the specific cancer genomes involved. Only five years ago, this approach would not have been technically feasible on the time scale of typical clinical trials, and it would also have been prohibitively expensive. Optimized cancer patient survival in clinical trials is now possible through multi-disciplinary approaches and high-throughput, low-cost analysis of cancer genomics [26-28,36], interactomics/proteomics [29-36] and epigenetics [36,37].

The critical part of all such optimized cancer clinical (OCC) trials involves learning how to deal with the drug-resistant malignant tumor subpopulations of cancer patients that were previously treated only with very limited success. The determination of the complete, individual cancer genomes present in such therapy-resistant cancer

***Corresponding author:** I.C. Baianu, AFC-NMR & NIR Microspectroscopy Facility, College of ACES, FSHN & NPRE Departments, University of Illinois at Urbana, Urbana, IL 61801, USA, E-mail: ibaianu@illinois.edu

Received February 17, 2012; **Accepted** February 21, 2012; **Published** February 24, 2012

Citation: Baianu IC (2012) Cancer Clinical Trials Optimization and Pharmacogenomics. J Clin Trials 1:e103. doi:10.4172/2167-0870.1000e103

cell subpopulations [1] is therefore critical for the success of optimized clinical trials that maximize the survival rates of the cancer patients involved in the OCC trials.

References

1. Stratton MR, Campbell PJ, Futreal PA (2009) The cancer genome. Nature 458: 719-724.
2. Baianu IC (2011) Translational Oncogenomics and Human Cancer Interactomics: Advanced Techniques and Complex System Dynamic Approaches. In: Mahmood A Mahdavi (Editors) Bioinformatics-Trends and Methodologies. InTech 473-510.
3. Baianu IC, Costescu D, You T (2004) Near Infrared / Fluorescence Microspectroscopy, Infrared Chemical Imaging and High-Resolution NMR Analysis of Soybean Seeds, Somatic Embryos and Single Cancer Cells. In: Luthria DL (Editor) Oil Extraction and Analysis. AOCS Press, USA 241-273.
4. Baianu IC (2012) Clinical Trials in Cancer and Pharmacogenomics: A Critical Evaluation. J Clin Trials.
5. Barabási AL, Oltvai ZN (2004) Network biology: understanding the cell's functional organization. Nat Rev Genet 5: 101-113.
6. Ross DT, Scherf U, Eisen MB, Perou CM, Rees C, et al. (2000) Systematic variation in gene expression patterns in human cancer cell lines. Nat Genet 24: 227-235.
7. Dobashi Y, Goto A, Fukayama M (2004) Overexpression of Cdk4/Cyclin D1, a possible mediator of apoptosis and an indicator of prognosis in human primary lung carcinoma. Intl J Cancer 110: 532-541.
8. Jonsson PF, Bates PA (2006) Global topological features of cancer proteins in the human Interactome. Bioinformatics 22: 2291-2297.
9. Jonsson PF, Cavanna T, Zicha D, Bates PA (2006) Cluster analysis of networks generated through homology: automatic identification of important protein communities involved in cancer metastasis. BMC Bioinformatics 7: 2.
10. Johnston SR, Hickish T, Ellis P, Houston S, Kelland L, et al. (2000) A phase II study of the farnesyl transferase inhibitor R115777 in patients with advanced breast cancer. Proc Am Soc Clin Oncol 19: 318.
11. Moyer JD, Barbacci EG, Iwata KK, Arnold L, Boman B, et al. (1997) Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. Cancer Res 57: 4838-4848.
12. Muraoka RS, Lenferink AE, Simpson J, Brantley DM, Roebuck LR, et al. (2001) Cyclin-dependent kinase inhibitor p27kip1 is required for mouse mammary gland morphogenesis and function. J Cell Biol 153: 917-931.
13. Neal DE, Marsh C, Bennett MK, Abel PD, Hall RR, et al. (1985) Epidermal-growth-factor receptors in human bladder cancer: comparison of invasive and superficial tumours. Lancet 1: 366-368.
14. Negoro S, Nakagawa K, Fukuoka M, Kudoh S,Tamura T, et al. (2001) Final results of a phase I intermittent dose-escalation trial of ZD1839 ('Iressa') in Japanese patients with various solid tumors. Proc Am Soc Clin Oncol 20: 1292.
15. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, et al. (2000) Molecular portraits of human breast tumors. Nature 406: 747-752.
16. Sausville EA, Elsayed Y, Monga M, Kim G (2003) Signal transduction-directed cancer treatments. Annu Rev Pharmacol Toxicol 43: 199-231.
17. Schellens JH, de Klerk G, Swart M, Palmer P, Bol C, et al. (2000) Phase I and pharmacologic study with the novel farnesyltransferase inhibitor R115777. Proc Am Soc Clin Oncol 19: 715.
18. Sekulić A, Hudson CC, Homme JL, Yin P, Otterness DM, et al. (2000) A direct linkage between the phosphoinositide 3-kinase-AKT signaling pathway and the mammalian target of rapamycin in mitogen-stimulated and transformed cells. Cancer Res 60: 3504-3513.
19. Sirotnak FM, Zakowski MF, Miller VA, Scher HI, Kris MG (2000) Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by coadministration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase. Clin Cancer Res 6: 4885-4892.
20. Somasundaram K, Zhang H, Zeng YX, Houvras Y, Peng Y, et al. (1997) Arrest of the cell cycle by the tumour-suppressor BRCA1 requires the CDK-inhibitor p21 WAF1/CiP1. Nature 389: 187-190.
21. Weinstein JN (2000) Pharmacogenomics-Teaching Old Drugs New Tricks. N Engl J Med 343: 1408-1409.
22. Yu C, Dent P, Grant S (2002) Pharmacologic PI3 kinase inhibitors interact in a highly synergistic manner with the cyclin-dependent kinase flavopiridol to induce mitochondrial damage, caspase activation, and apoptosis in human leukemia cells. Proc Am Assoc Cancer Res 43: 2983.
23. Shapiro GI, Supko JG, Patterson A, Lynch C, Lucca J, et al. (2001) A phase II trial of the cyclin-dependent kinase inhibitor flavopiridol in patients with previously untreated stage IV non-small cell lung cancer. Clin Cancer Res 7: 1590-1599.
24. Prisecaru V, Baianu IC (2004) Cell Cycling Models of Carcinogenesis: A Complex Systems Analysis 1-22.
25. Senderowicz AM, Sausville EA (2000) Preclinical and clinical development of cyclin-dependent kinase modulators. J Natl Cancer Inst 92: 376-387.
26. Snijders AM, Nowak N, Segraves R, Blackwood S, Brown N, et al. (2001) Assembly of microarrays for genome-wide measurement of DNA copy number. Nat Genet 29: 263-264.
27. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 98: 10869-10874.
28. Silverman L, Campbell R, Broach JR (1998) New assay technologies for high throughput screening. Curr Opin Chem Biol 2: 397-403.
29. Zhu H Snyder M (2001) Protein arrays and microarrays. Curr Opin Chem Biol 5: 40-45.
30. Sidransky D (2002) Emerging molecular markers of cancer. Nat Rev Cancer 2: 210-219.
31. Senior K (1999) Fingerprinting disease with protein chip arrays. Mol Med Today 5: 326-327.
32. Klinge, Owman (1990) Ultrasensitive detection of single molecules by fluorescence correlation spectroscopy. In: Rigler R, Widengren J (Editors) Single molecule spectroscopy in chemistry, physics and biology, Springer, USA 180-184.
33. Yu J, Zhang L, Hwang PM, Rago C, Kinzler KW, et al. (1999) Identification and classification of p53-regulated genes. Proc Natl Acad Sci U S A 96: 14517-14522.
34. Pinkel D, Segraves R, Sudar D, Clark S, Poole I, et al. (1998) High resolution analysis of DNA copy number variation using comparative genomic hybridization to microarrays. Nat Genet 20: 207-211.
35. Yu X, Wu LC, Bowcock AM, Aronheim A, Baer R (1998) The C-terminal (BRCT) domains of BRCA1 interact in vivo with CtIP, a protein implicated in the CtBP pathway of transcriptional repression. J Biol Chem 273: 25388-25392.
36. Baianu IC (2011) Translational Oncogenomics and Human Cancer Interactome Networks. Nature Precedings: 1-59.
37. Plass C (2002) Cancer epigenomics. Hum Mol Genet 11: 2479-2488.