



Strategies for Multiple Signalling Inhibition

G. Tortora, R. Bianco & G. Daniele

To cite this article: G. Tortora, R. Bianco & G. Daniele (2004) Strategies for Multiple Signalling Inhibition, Journal of Chemotherapy, 16:sup4, 41-43, DOI: [10.1179/joc.2004.16.Supplement-1.41](https://doi.org/10.1179/joc.2004.16.Supplement-1.41)

To link to this article: <https://doi.org/10.1179/joc.2004.16.Supplement-1.41>



Published online: 13 Dec 2013.



Submit your article to this journal [↗](#)



Article views: 10



View related articles [↗](#)



Citing articles: 11 View citing articles [↗](#)

Strategies for Multiple Signalling Inhibition

G. TORTORA - R. BIANCO - G. DANIELE

Division of Medical Oncology and Laboratory and Clinical Unit of Molecular Therapy, Department of Molecular and Clinical Endocrinology and Oncology, University of Naples "Federico II", Naples, Italy.

Correspondence: Via Pansini 5, 80131 Napoli, Italy.
Tel. +39081.7462061; Fax. +39081.2203147; E-mail: tortora@unina.it

Summary

Cancer cells hyperactivate signalling molecules, including EGFR, Akt and the angiogenic factor VEGF to escape apoptosis, thus contributing also to resistance to treatment. While single signalling inhibitors have produced limited advantages in clinical trials, their combination with conventional treatments is more effective; however, the rate of responses is generally around 20%. A major limitation is represented by the activation of escape pathways, due to an intensive cross-talk and redundancy of signals in the transduction network. A novel and more rational approach is the combination of multiple signalling inhibitors, according to the molecular context of disease, in combination with selected conventional treatments.

Key words: EGFR, therapeutic strategies, VEGF.

Cancer cells have altered expression/function of signalling molecules, which control cell cycle and DNA repair (genomic signals), and of growth and angiogenic factors (survival factors) in order to escape the physiologic apoptosis that would be naturally induced by their gross genomic alterations. In the past few years much evidence has demonstrated that these same molecules are also involved in preserving cancer cells from treatment-induced apoptosis, thus contributing to resistance to treatment, tumor relapse and progression. Several molecules among these signal transducers have been recognized as potentially relevant targets for selective agents, including the receptors EGFR, erbB-2, and endothelin A (ET_A); the antiapoptotic proteins bcl-2, bcl-xL and Akt; the angiogenic factor VEGF and its receptors Flt-1 and Flk-1/KDR. EGFR plays multiple roles in signal transduction as it is directly involved in cell proliferation, apoptosis and angiogenesis and is implicated in resistance to treatment, thus representing a prototype of multifunctional molecular target for epithelial cancers (Figure 1)¹. For these reasons EGFR inhibitors are among the most investigated agents and a large number of clinical trials with both monoclonal antibodies and small molecules targeting the EGFR kinase domain have been conducted in patients affected by different tumors. In the

vast majority of studies single EGFR inhibitors have produced responses in heavily pretreated patients but, generally, the rate of response is rarely higher than 10%¹. This same activity has been reported also for agents targeting ErbB-2, VEGF, VEGF receptors and many other signalling molecules, when used as single agents.

A more advantageous approach is the combination of a signalling inhibitor with conventional treatments, based on the hypothesis that, following treatment with chemo- or radiotherapy, cells activate survival pathways that, if efficiently blocked, would force cells to enter apoptosis. Preclinical studies have confirmed the potential of such a strategy and translation into the clinic has shown encouraging results¹. In spite of the early negative results obtained with the EGFR tyrosine kinase inhibitors gefitinib and erlotinib in combination with standard treatment in non small cell lung cancer^{2,3}, the combination of standard regimens with monoclonal antibodies targeting either EGFR (cetuximab) or VEGF (bevacizumab) has shown relevant advances in the treatment of patients with metastatic colorectal cancer (MCRC)^{4,5}. Also the addition of bevacizumab to the least active treatment, 5-FU + folate, has provided an advantage in MCRC as compared to chemotherapy alone⁵. Similar benefit has been

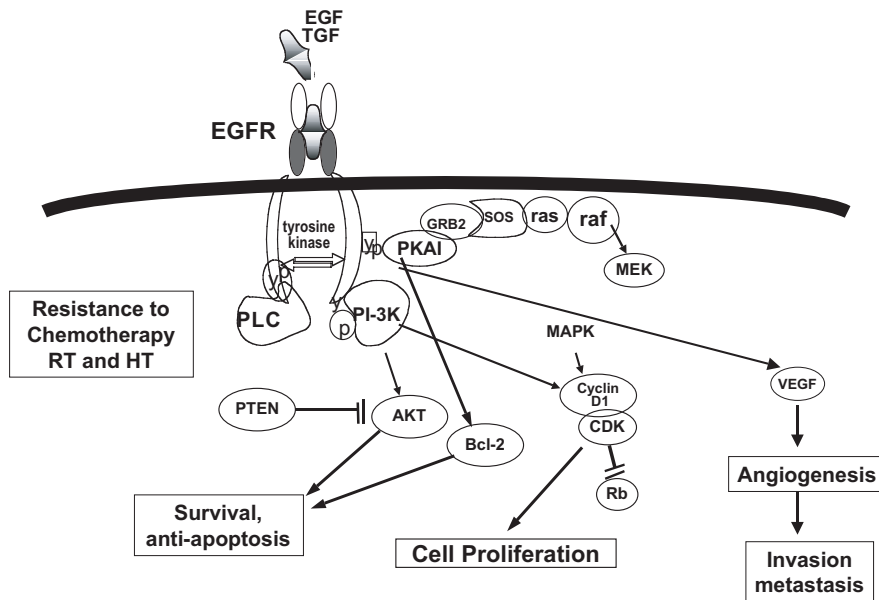


FIGURE 1 - Pleiotropic effects of EGFR activation

demonstrated with EGFR inhibitors combined with radiotherapy in other diseases, including squamous tumors of the head and neck ¹.

Several ongoing clinical trials are now exploring these combinations in the adjuvant setting rather than in the late stages of disease to obtain an impact on disease free survival. However, in the great majority of cases, the rate of responses in the metastatic setting is generally around 20% and several potential limits of such strategy are now emerging. One limit is represented by the correct sequence of treatment, since several trials conducted to date have shown a reciprocal interference at the molecular level between the targeted agent and the cytotoxic treatment ⁶. Another and more relevant problem lies in the cross-talk and the consequent redundancy of signals present in the transduction network of cancer cells. This implies that the blockade of an even relevant signalling molecule results frequently in the activation of other signalling pathways that represent an escape toward cell proliferation ¹. Therefore, it can be predicted that the combination of a single signalling inhibitor with the conventional treatment may cause only a temporary success, lasting until a major escape pathway becomes prominent. In the case of EGFR and erbB-2 inhibitors, preclinical and pharmacodynamic clinical studies have demonstrated this hypothesis, highlighting the role played by the insulin-like growth factor receptor (IGFR-1) in resistance to trastuzumab ⁷ and of Akt, MAPK and VEGF as escape pathways following the blockade of EGFR ^{1,8,9}.

We have recently provided evidence that human colon cancer cells xenografted in nude mice that have acquired resistance to EGFR inhibitors, monoclonal antibodies as well as small molecules, escape

the EGFR blockade through the overexpression and function of MAPK and VEGF ¹⁰. The recent synthesis and development of a new class of agents able to interfere with multiple targets has initially brought optimism on the possibility to control also the escape pathways. Most of these multitargeted agents downregulate two or more growth and angiogenic factor receptors, including KDR, EGFR, PDGFR, KIT and FLT3. Among them, SU11248, PTK787 and ZD6474 have shown a good toxicity profile and activity in early clinical trials, but they were unable to produce a large percent of responses when used alone, suggesting once again their rational combination with chemo- and radiotherapy.

On these bases, to achieve major advancement, a rational novel therapeutic strategy should accomplish the blockade of selected multiple targets that are involved in critical "nodal" points of the escape pathways, by more or less selective inhibitors, in combination with selected cytotoxics or radiotherapy able to disrupt cellular structures involving molecules functionally-related to those affected by the targeted drugs. Possibly, signalling molecules involved in both, genomic and survival pathways, should be targeted at the same time (Figure 2). It can also be predicted that in certain circumstances, such as in tumors refractory to standard treatments but highly dependant on selected signalling pathways, it is possible that two specific targeted agents may have a major impact on tumor growth. For instance, this may be the case for renal cancer if treated with EGFR inhibitors in combination with VEGF/VEGF receptor inhibitors.

The clinical implementation of these principles must take into consideration: a) the evaluation of the clinical (disease, stage) and molecular context in

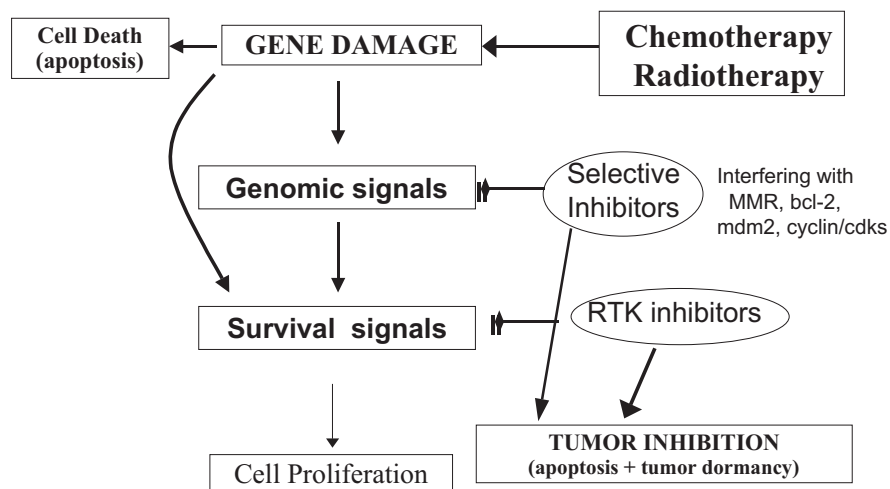


FIGURE 2 - Therapeutic strategies

which drugs are used; b) the determination of the expression of escape and resistance molecules (with classical and/or postgenomic techniques); c) the combination of molecular and conventional drugs with different and complimentary targets, evaluating rationally the sequence and the schedule of administration of the different agents.

REFERENCES

- ¹ Ciardiello F, Tortora G. Epidermal growth factor receptor (EGFR) as a target in cancer therapy: understanding the role of receptor expression and other molecular determinants that could influence the response to anti-EGFR drugs. *Eur J Cancer* 2003; 39: 1348-1354.
- ² Giaccone G, Johnson DH, Manegold C, *et al.* Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial-INTACT 1. *J Clin Oncol* 2004; 22: 777-784.
- ³ Dancey JE, Freidlin B. Targeting epidermal growth factor receptor - are we missing the mark? *Lancet* 2003; 362: 62-64.
- ⁴ Cunningham D, Humblet Y, Siena S, *et al.* A randomized comparison of cetuximab monotherapy and cetuximab

plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351: 337-345.

⁵ Hurwitz H, Fehrenbacher L, Novotny W *et al.* Bevacizumab plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350: 2335-2342.

⁶ Arteaga CL, Baselga J. Clinical trial design and endpoints for epidermal growth factor receptor-targeted therapies: implications for drug development and practice. *Clin Cancer Res* 2003; 9: 1579-89.

⁷ Lu Y, Zi X, Zhao Y, Mascarenhas D, Pollak M. Insulin-like growth factor-I receptor signaling and resistance to trastuzumab (Herceptin). *J Natl Cancer Inst* 2001; 93: 1852-1857.

⁸ Bianco R, Shin I, Ritter C, *et al.* Loss of PTEN/MMAC1/TEP in EGF receptor-expressing tumor cells counteracts the antitumor action of EGFR tyrosine kinase inhibitors. *Oncogene* 2003; 22: 2812-2822.

⁹ Vitoria-Petit A, Crombet T, Jothy S, *et al.* Acquired resistance to the antitumor activity of epidermal growth factor receptor-blocking antibodies in vivo: a role for altered tumor angiogenesis. *Cancer Res* 2001; 61: 5090-5101.

¹⁰ Ciardiello F, Bianco R, Caputo R, *et al.* Antitumor activity of ZD6474, a small molecule VEGF receptor tyrosine kinase inhibitor, in human cancer cells with acquired resistance to EGF receptor-targeted drugs. *Clin Cancer Res* 2004; 10: 784-793.