Editorial

Skin as a Surrogate Tissue for Pharmacodynamic End Points: Is It Deep Enough?

Jose Baselga
Vall d’Hebron University Hospital, Universidad Autonoma de Barcelona, Barcelona, Spain

Introduction
As the number of molecular-targeted agents under clinical development keeps growing, it is becoming increasingly evident that it will be far more complex to demonstrate clinical benefit with these agents than with conventional cytotoxic agents (1, 2). The reason for this new paradox in clinical research lies in the own nature of targeted therapy: these agents are predicted to work only in a subpopulation of patients whose tumors growth and/or survival are driven either by the target or target-dependent processes. This is best exemplified in the case of erbB2-overexpressing breast tumors that are sensitive to the anti-erbB2 monoclonal antibody trastuzumab (Herceptin) and with the remarkable success of STI571 (Gleevec) in the treatment of chronic myelogeneous leukemia and gastrointestinal stromal tumors. In addition, with these agents, it is difficult to identify the optimal biological dose. In most occasions, there should be no need to dose escalate until reaching the maximally tolerated dose. Pharmacokinetic end points alone might also be insufficient to identify the best dose and schedule unless a solid correlation could be demonstrated with in vivo effect in the target. There is, therefore, a growing consensus that the definition of the optimal biological dose of a targeted therapy should be based on the demonstration in vivo of the desired biochemical effect on the target molecule.

So, how are we going to resolve these challenges that could endanger the development of this promising class of agents? First, there is no substitute for good preclinical models as again exemplified with trastuzumab (3–5). Second, there is a need to study in patients the effects of these agents on their targets by performing careful pharmacodynamic evaluations in the tumor or in appropriate surrogate tissues. The concept behind pharmacodynamic studies is that by (sequentially) analyzing the effects of a given therapy on a patient’s tissue, we might be able to determine the expression level of the target and to monitor the effects of a given agent on its molecular target. If in addition, treatment with the study agent results in a modulation of expression of genes related to the target, pharmacodynamic studies could also be instrumental in the identification of the subpopulation of patients that may derive benefit from this therapy.

The ideal tissue to perform pharmacodynamic studies is the own tumor. However, taking in consideration the difficulties to perform sequential tumor biopsies, the use of surrogate tissues is being explored instead. In choosing appropriate surrogate tissues, a series of conditions would be required: (a) the target and/or markers downstream of the target have to be expressed in the studied tissue; (b) the target and/or additional markers have to be regulated (inhibited) by the experimental therapy; and (c) in preclinical model, a tight correlation has to exist between the optimal therapeutic effect and the observed changes in the selected biomarker(s). An optional but preferred attribute for a surrogate tissue is to be of easy access to allow for repeated sampling. In this setting, there is hardly an easier tissue to study than peripheral blood cells or, as we are reviewing here, the skin.

In series of early studies with anti-EGFR2 therapies, the skin was proposed as a potential surrogate tissue for EGFR inhibition in vivo (6, 7). The skin was selected as the target tissue, in addition to its easy access, because of the established role of the EGFR in renewal of the dermis (8, 9). In normal adult human skin, the EGFR is strongly expressed in keratinocytes and in cells of eccrine and sebaceous glands. In an initial study with the anti-EGFR low molecular weight tyrosine kinase inhibitor, ZD1839 (Iressa), sequential skin biopsies demonstrated changes in phosphorylation of EGFR, mitogen-activated protein kinase, and STAT-3, as well as in the levels of the cyclin-dependent kinase inhibitor 27Kip1, the proliferation marker Ki67, and skin maturation markers (7). In the current issue of the journal, an important confirmatory study is being presented including PKI-166 (11), CI-1033 (12), and with the monoclonal antibody trastuzumab (Herceptin) and with the remarkable success of STI571 (Gleevec) in the treatment of chronic myelogeneous leukemia and gastrointestinal stromal tumors. In addition, with these agents, it is difficult to identify the optimal biological dose. In most occasions, there should be no need to dose escalate until reaching the maximally tolerated dose. Pharmacokinetic end points alone might also be insufficient to identify the best dose and schedule unless a solid correlation could be demonstrated with in vivo effect in the target. There is, therefore, a growing consensus that the definition of the optimal biological dose of a targeted therapy should be based on the demonstration in vivo of the desired biochemical effect on the target molecule.

So, how are we going to resolve these challenges that could endanger the development of this promising class of agents? First, there is no substitute for good preclinical models as again exemplified with trastuzumab (3–5). Second, there is a need to study in patients the effects of these agents on their targets by performing careful pharmacodynamic evaluations in the tumor or in appropriate surrogate tissues. The concept behind pharmacodynamic studies is that by (sequentially) analyzing the effects of a given therapy on a patient’s tissue, we might be able to determine the expression level of the target and to monitor the effects of a given agent on its molecular target. If in addition, treatment with the study agent results in a modulation of expression of genes related to the target, pharmacodynamic studies could also be instrumental in the identification of the subpopulation of patients that may derive benefit from this therapy.

The ideal tissue to perform pharmacodynamic studies is the own tumor. However, taking in consideration the difficulties to perform sequential tumor biopsies, the use of surrogate tissues is being explored instead. In choosing appropriate surrogate tissues, a series of conditions would be required: (a) the target and/or markers downstream of the target have to be expressed in the studied tissue; (b) the target and/or additional markers have to be regulated (inhibited) by the experimental therapy; and (c) in preclinical model, a tight correlation has to exist between the optimal therapeutic effect and the observed changes in the selected biomarker(s). An optional but preferred attribute for a surrogate tissue is to be of easy access to allow for repeated sampling. In this setting, there is hardly an easier tissue to study than peripheral blood cells or, as we are reviewing here, the skin.

In series of early studies with anti-EGFR2 therapies, the skin was proposed as a potential surrogate tissue for EGFR inhibition in vivo (6, 7). The skin was selected as the target tissue, in addition to its easy access, because of the established role of the EGFR in renewal of the dermis (8, 9). In normal adult human skin, the EGFR is strongly expressed in keratinocytes and in cells of eccrine and sebaceous glands. In an initial study with the anti-EGFR low molecular weight tyrosine kinase inhibitor, ZD1839 (Iressa), sequential skin biopsies demonstrated changes in phosphorylation of EGFR, mitogen-activated protein kinase, and STAT-3, as well as in the levels of the cyclin-dependent kinase inhibitor 27Kip1, the proliferation marker Ki67, and skin maturation markers (7). In the current issue of the journal, an important confirmatory study is being presented including OSI-774 (Tarceva), another anti-EGFR tyrosine kinase inhibitor (10). In this elegant work by Malik et al. (10), they sequentially collected skin specimens from 28 patients treated with OSI-774 at doses ranging from 25 to 200 mg/day. Using both a semiquantitative and an absorbance automated method, they observed a significant decrease in phospho-EGFR and an up-regulation of p27. Interestingly, the effects seen on p27 were dose related, although given the high level of interpatient variability of steady-state concentrations (Css) with this class of anti-EGFR agents, it might have been preferred to study potential correlations with Css rather that with dose levels. In addition, to the skin data with ZD1839 and OSI-774, there is also preliminary confirmatory results with other anti-EGFR agents, including PKI-166 (11), CI-1033 (12), and with the monoclonal antibody EMD72000 (13).

The combined analysis of these studies, conducted with different agents and independent investigators, should be taken as sufficient evidence in support of the skin as a valid surrogate tissue to study EGFR inhibition in nontumoral cells in patients. As an extension of this work, the skin may also be a valid

Received 4/16/03; accepted 4/22/03.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 To whom requests for reprints should be addressed, at Medical Oncology Service, Vall d’Hebron University Hospital, P. Vall d’Hebron 119-129, 08035 Barcelona, Spain.

2 The abbreviation used is: EGFR, epidermal growth factor receptor.
surrogate tissue for other novel targets and similar studies as the one conducted by Malik et al. (10) could be performed with other classes of agents. An important question not answered by any of these studies is the degree of correlation between the changes that occur in the skin and those ongoing in the tumor. It is possible that blood flow may be different in the skin and the heterogeneous and at times poorly vascularized tumor. This would result in less drug reaching the tumor. In addition, even if similar amounts of the agent reach the tumor and the target is inhibited as desired, the downstream effects of this inhibition may be different. As an example, tumors frequently exhibit mutations that lead to constitutive activation of the phosphatidylinositol 3'-kinase-akt pathway (14), which could render cells independent of upstream EGFR inhibition.

In conclusion, let us address the question raised in the title: should we be satisfied by performing pharmacodynamic studies in the skin? The short answer is that we should not limit our pharmacodynamic studies to skin biopsies. Sequential skin biopsies have been shown to be useful at showing target (EGFR) inhibition in vivo, and they hopefully will also be useful with other targets expressed in the skin. The skin, by its ease of access, will enable us to optimize our methods to detect inhibition of these targets and their corresponding pathways in vivo. Skin studies may also provide broad indications of the appropriate dose range and the best scheduling. However, at the end of the day, we will have to look in the tumor. Given the complexity of these agents, if we could incorporate tumor pharmacodynamic end points in the early phases of drug development, it would enable us to move ahead with greater confidence and better chances of success.

References


13. Taberner, J., Rojo, F., Jimenez, E., Montaner, I., Santome, L., Guix, M., Rosen, Kovar, A., Viaplana, I., and Baselga, J. A Phase I pharmacokinetic (PK) and serial tumor and skin pharmacodynamic (PD) study of weekly, every 2 weeks or every 3 weeks 1-hour (h) infusion EMD72000, an humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody, in patients (p) with advanced tumors known to overexpress the EGFR. Eur. J. Cancer, 38 (Suppl. 7): 69, 2002.

Skin as a Surrogate Tissue for Pharmacodynamic End Points: Is It Deep Enough?

Jose Baselga


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/9/7/2389

Cited articles
This article cites 12 articles, 4 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/9/7/2389.full.html#ref-list-1

Citing articles
This article has been cited by 10 HighWire-hosted articles. Access the articles at:
/content/9/7/2389.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.