EUROPEAN JOURNAL OF CANCER 42 (2006) 808–810

available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

Editorial Comment

With a little help from small friends: Enhanced chemotherapeutic effects with imatinib

*Stefan Sleijfer**

Department of Medical Oncology, Erasmus University Medical Center, Daniel den Hoed Cancer Center, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 17 December 2005
Accepted 20 December 2005
Available online 13 March 2006

The tyrosine kinase inhibitors (TKI), the "nibs", such as imatinib, erlotinib, sorafenib, sunitinib and several others form a valuable addition to the armamentarium against solid malignancies. Imatinib has rapidly become standard treatment for patients with unresectable gastrointestinal stromal tumours (GIST), erlotinib improves survival in patients with metastatic non-small cell lung cancer (NSCLC) who have failed one prior line of chemotherapy, and approval for sorafenib and sunitinib as second-line treatment for advanced renal cell carcinoma is pending. Furthermore, numerous trials with these and other TKI's in many tumour entities are currently ongoing. Indeed, in a short period of time, these small molecules, given as monotherapy, have acquired an established role in the treatment of solid malignancies and it is likely that their role will soon gain even greater importance. The next challenge is to apply these compounds in combination with other anti-tumour drugs.

Although the first randomized trials which evaluated the combination of chemotherapy with TKI's targeting the epithelial growth factor-receptor (EGF-R) yielded disappointing outcomes in NSCLC,[1,2] there are several reasons why the application of conventional chemotherapeutic agents and TKI's directed towards targets other than EGF-R still remains worthwhile exploring. In this issue of *The European Journal of Cancer*, a phase I study evaluating the combination of imatinib with either gemcitabine or doxorubicin is reported.[3] Imatinib (Glivec®, Gleevec™) is a TKI of several proteins including c-kit, c-abl, Bcr-Abl, ARG (Abl-related tyrosine kinase), LCK, and the platelet-derived growth factor-receptor (PDGF-R). Preferably, when drugs are combined in oncology, there are several prerequisites to be met, the most essential ones being single agent efficacy, a different mode of action, non-overlapping toxicity, and synergistic interaction. In solid tumours, imatinib is currently known to exert anti-tumour activity against only GIST and dermatofibrosarcoma protuberans. However, theoretically other prerequisites are fulfilled. It is clear that imatinib and conventional chemotherapeutic drugs such as doxorubicin and gemcitabine differ in their mechanisms of action. Also their toxicity profiles do not overlap. Neutropenia and cardiomyopathy are the most feared untoward sequelae of doxorubicin, while gemcitabine monotherapy has a relatively mild toxicity profile with transient hepatitis, neutro- and thrombopenia as the most important ones. Imatinib induces grade 3–4 neutropenia, thrombopenia

* Tel.: +31 10 439 1906; fax: +31 10 439 1003.
E-mail address: s.sleijfer@erasmusmc.nl.
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.12.019

or hepatitis in approximately 5% of the patients and is not associated with cardiomyopathy. Furthermore, imatinib exhibited synergistic anti-tumour activity combined with several distinct classes of chemotherapy in vitro.[4] There are several potential mechanisms that may underlie this interaction. Activation of PDGF-R can result in higher levels of Bcl-2, a well-known anti-apoptotic factor.[5] As imatinib inhibits PDGF-R-mediated actions, it may lower Bcl-2 levels thereby rendering tumour cells more prone to apoptotic triggers such as gemcitabine or doxorubicin. In addition, expression of drug-efflux pumps such as P-glycoprotein confers resistance against doxorubicin. Since imatinib is also a substrate for and an inhibitor of P-glycoprotein,[6] imatinib may increase intracellular levels of doxorubicin resulting in greater anti-tumour effects. Additionally, a way by which imatinib may augment anti-tumour effects in vivo is through reduction of the interstitial fluid pressure of tumours. Compared to adjacent tissues, many tumours are featured by increased interstitial fluid pressure, which hinders drug penetration into these tumours. Inhibition of PDGF-R by imatinib reduces this pressure facilitating uptake of concomitantly administered drugs.[7]

Thus collectively, there are several reasons which make the combination of imatinib with either gemcitabine or doxorubicin appealing.

However, in the study by George and colleagues,[3] imatinib combined with doxorubicin as well as gemcitabine induced toxicity that was deemed unacceptable, even at relatively low doses of all three drugs applied. Imatinib concomitantly administered with gemcitabine resulted in predefined dose-limiting toxicities (DLT) in terms of neutropenia, thrombopenia, and fatigue. The combination with doxorubicin yielded DLT's consisting of neutropenia, vomiting, and an asymptomatic decrease in left ventricular ejection fraction after 9 cycles of treatment in one patient, which was also regarded as dose-limiting.

It is unclear why these combinations were so poorly tolerated. Unfortunately, no pharmacokinetic analyses were performed, a pivotal part of phase I studies. Although imatinib, doxorubicin, and gemcitabine are thought to be metabolised through different systems, as mentioned before, both doxorubicin and imatinib are substrates for P-glycoprotein. Previously, P-glycoprotein blockade has been demonstrated to increase the area under the plasma concentration–time curve (AUC) of doxorubicin, and its metabolite doxorubicinol resulting in augmented toxicity.[8] Accordingly, imatinib may lead to higher levels of doxorubicin accounting for the increased toxicity. This might have also resulted in the case of cardiomyopathy encountered in the study, although it occurred after a cumulative doxorubicin dose of 450 mg/m^2, a dose not uncommonly associated with cardiomyopathy. An alternative explanation for the occurrence of this particular adverse event might be through effects on the interstitial fluid pressure. Recently, an unexpected high rate of cardiomyopathy was seen in a study assessing doxorubicin concurrently given with bevacizumab, a monoclonal antibody against the vascular endothelial growth factor-receptor.[9] Bevacizumab is not known to affect pharmacokinetics of chemotherapeutic drugs but similar to imatinib, is able to reduce interstitial fluid pressure, suggesting that doxorubicin is not the most suitable drug to combine with compounds decreasing interstitial fluid pressure.

Pharmacokinetic effects are unlikely to account for the enhanced toxicity seen in the gemcitabine-containing combination. In another study, currently only available in abstract form, imatinib did not affect pharmacokinetics of gemcitabine.[10] Since in this study the combination of imatinib and gemcitabine was also unfeasible, this strongly suggests that the pronounced effects from this combination occur at cellular level and are due to yet unravelled pharmacodynamic mechanisms. A potential mechanism might be that imatinib shifts the balance between pro- and anti-apoptotic proteins towards the former rendering cells more sensitive to chemotherapy.[4] To further characterise this, healthy tissue, for example bone marrow, should be examined before and after imatinib treatment.

Nevertheless, the aggravated effects on healthy tissues and organs as found in George and colleagues' study convincingly show that chemotherapeutic effects can be enhanced by TKI's. However, the precise mechanisms underlying the enhanced effects when combining imatinib with doxorubicin and gemcitabine remain obscure. It is of great importance to elucidate these in order to identify means to attenuate the toxicity. Therefore, phase I studies including pharmacokinetic and pharmacodynamic evaluations must be conducted before subjecting combinations of TKI's and chemotherapy to further clinical testing. In addition, for instance by taking tumour biopsies, attempts must be made to reveal whether or not chemotherapeutic effects are also potentiated by TKI's at tumour cell level. If so, enhancement of chemotherapeutic effects with a little help from these small molecules is indeed a promising approach.

Conflict of interest statement

None declared.

REFERENCES

1. Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial-INT ACT 1. *J Clin Oncol* 2004;**22**:777–84.
2. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2005;**23**:5892–9.
3. George S, Desai J, Eder JP, et al. Selective kinase inhibition with daily imatinib intensifies toxicity of chemotherapy in patients with solid tumours. *Eur J Cancer*, this issue, doi:10.1016/j.ejca.2005.12.010.
4. Fang G, Kim CN, Perkins CL, et al. CGP57148B (STI-571) induces differentiation and apoptosis and sensitizes Bcr-Abl-positive human leukemia cells to apoptosis due to antileukemic drugs. *Blood* 2000;**96**:2246–53.
5. Aimakajornboon N, Szerlip NJ, Gozal E, Anonetapipat JW, Gozal D. In vivo PDGF beta receptor activation in the dorsocaudal brainstem of the rat prevents hypoxia-induced apoptosis via activation of Akt and BAD. *Brain Res* 2001;**895**:111–8.

6. Mahon FX, Belloc F, Lagarde V, et al. MDR1 gene overexpression confers resistance to imatinib mesylate in leukaemia cell line models. *Blood* 2003;**101**:2368–73.
7. Pietras K, Stumm M, Hubert M, et al. STI571 enhances the therapeutic index of epothilone B by a tumour-selective increase of drug uptake. *Clin Cancer Res* 2003;**9**:3779–87.
8. Giaccone G, Linn SC, Welink J, et al. A dose-finding and pharmacokinetic study of reversal of multidrug resistance with SDZ PSC 833 in combination with doxorubicin in patients with solid tumours. *Clin Cancer Res* 1997;**3**:2005–15.
9. D'Adamo DR, Anderson SE, Albritton K, et al. Phase II of doxorubicin and bevacizumab for patients with metastatic soft-tissue sarcomas. *J Clin Oncol* 2005;**23**:7135–42.
10. Poplin E, Gharibo M, Rodriguez L, et al. Phase I study of imatinib mesylate and gemcitabine in patients with refractory solid tumour malignancy. *Proc Am Soc Clin Oncol* 2004;**24**:3100.