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Editorial Comment

OncoloGIST, BioloGIST, RadioloGIST: the big impact on the field of oncology of a molecularly-targeted therapy designed to treat a rare disease

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The field of oncology is now in a period of enlightenment, linking scientific and clinical progress. The basic principles of cancer biology, which have been systematically explored over the past three decades, are now being translated into effective, new clinical therapeutic strategies. The paradigm of this work has been the development of selective tyrosine kinase inhibiting agents, of which Imatinib (Glivec^{R}/Gleevec^{TM}, made by Novartis Pharmaceuticals of Basel Switzerland) is the most studied and clinically developed example. Two papers, published in this issue of the *European Journal of Cancer* [1,2], further demonstrate the impact this agent has had on the fundamental principles of clinical investigation and translational research.

Imatinib is a translational product of many decades of insightful work into the molecular biology of oncogenes, leukaemia and signal transduction. Drs Brian Druker, Nicholas Lyden, Alex Matter and colleagues at Novartis, in association with other investigators worldwide, proved the principle that inhibition of the uncontrolled tyrosine kinase activity of the chimeric BCR-ABL oncoprotein could lead to clinical and molecular remissions of leukaemias in which this oncoprotein was present. This has revolutionised the treatment of chronic myeloid leukaemia (CML) and molecularly-related haematological malignancies.

The impact of Imatinib has been expanded beyond the BCR-ABL target. Specifically, insights were made from the laboratory study of Hirota and colleagues in Japan on a solid tumour, gastrointestinal stromal tumour (GIST) [3], a form of sarcoma totally unconnected with leukaemia or the oncogenic signalling of BCR-ABL. This group detected an uncontrolled mutant form of a completely different tyrosine kinase known as KIT. In their small, but important, study, they showed that most GIST cells had activated the KIT kinase in an uncontrolled manner. Normal cells keep KIT and other kinase signalling under close regulatory supervision but, in GIST cells, this regulation does not exist. Clearly, this is analogous to the situation in CML, although involving an entirely different molecular pathway. Fortuitously, the same rationally-designed agent, Imatinib, had the ability to inhibit mutated KIT in GIST as well as the BCR-ABL products in CML [4,5]. Investigators were able to test these hypotheses in the clinic with mutated KIT as the target. The observations have been extremely consistent across multiple studies which have all shown that Imatinib possesses an unprecedented efficacy against most GISTs [6–8].

The extrapolation of the key message of this work to other forms of cancer provides a message of hope, as well as a strategically important caveat: find the key pathogenomic difference between the cancer and normal cell, therapeutically target it, and one should be able to make clinically extraordinary advances against that form of cancer.

This sounds simple and elegant. However, in truth, this process will continue to be a complex undertaking, since we can assure ourselves only occasionally that a specific molecular abnormality is truly a 'key' difference between the cancer and normal cell. Cancer cells have many differences that distinguish them from normal cells [9]. The difficulty is in identifying which of these many differences would be necessary and sufficient to target in order to see clinical benefits in our patients.

In the paper by Verweij and colleagues, the success of the previously smaller study of the European Organisation for Research and Treatment of Cancer (EORTC) [7], which demonstrated the activity of Imatinib in GIST, is confirmed. However, these authors also caution that Imatinib is not a molecular panacea for all forms of cancer. Although there was a rationale for targeting forms of sarcoma other than GIST on the basis of the expression of the platelet-derived growth factor (PDGF) receptor, Imatinib showed little activity against other

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forms of sarcoma. This could mean that PDGF-R was simply not the activated and critical target in the forms of sarcoma chosen for this study. In fact, this is likely to be the case, since Imatinib has efficacy against dermatofibrosarcoma protuberans (DFSP), a subset of sarcoma with known mutational activation of the PDGF-R signalling pathway [10,11]. However, the activation of PDGF-R may not be the sole critical switch in other subsets of sarcomas, and therefore the inhibitory action of Imatinib may not lead to the dramatic results that have been noted in CML, GIST or DFSP.

None the less, there may still be clinical value in testing more completely the inhibition of the PDGF-R pathway in cancer. Other molecular rationales exist to support the potential of Imatinib in the treatment of other forms of cancer acting through novel physiological mechanisms, such as vascular permeability, which controls the pressure within the interstitial space [11,12]. The impact of this effect may be more subtle than the obvious and direct antitumour action of Imatinib in diseases such as GIST, in which a single molecular switch (a mutated kinase) has a disproportionate effect on the tumour cells, where inhibition of that kinase leads to tumour cell death or stasis. Our clinical investigations need to be sufficiently sensitive to detect important and developable activity in these other areas, and that is the focus of many ongoing clinical trials around the world. It is important to have appropriate expectations as this work develops, both for patients and their families, as well as their physicians. To that end, the paper by Verweij and colleagues adds a note of caution putting their data in perspective. The authors state that Imatinib alone will not yield the same dramatic anticancer results in all forms of sarcomas.

Another important impact of the work on Imatinib in cancer medicine is the exploration of different ways that investigators might visualise the effects of new agents in treated patients. There is a great need to have markers of drug effect so that translational clinical trials will obtain an accurate assessment of the target pathway in patients. In the work by Stroobants and colleagues, previous observations in GIST [6–8] are expanded to show that functional imaging with 18-fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning is an important marker showing the effect of Imatinib in GIST patients far earlier than conventional anatomical imaging with computerised tomography (CT) or magnetic resonance imaging (MRI) scans. The effect demonstrated is very reliable, providing confidence that early signals of activity will be clinically meaningful and will reflect a durable antitumour activity which benefits patients. The molecular mechanisms which underpin the effects of Imatinib on 18-FDG uptake and metabolism in GIST cells are still being worked out, but the practical impact for clinical investigators is already clear. PET is an important tool to accelerate drug development and testing in GIST, a disease in which PET is a reliable indicator of drug effect. The authors appropriately bring up many of the current challenges in the field of functional imaging, particularly noting that oncology will struggle without a global, agreed-upon scale to assess 'responses' in PET imaging. Quantitative as well as qualitative, tools to assess PET responses need to be developed so that investigators will be able to compare results around the world and so that global collaborations can move forward quickly and effectively.

The era of Imatinib and related molecularly-targeted therapeutics brings with it a new optimism and enthusiasm in oncology and drug development, as well as the validation of new exciting technologies such as PET scanning as reliable tools to speed up the important work of translating scientific advances into effective new therapies for our patients.

References

1. Verweij J, van Oosterom A, Blay J-Y, *et al*. Imatinib mesylate (STI-571 Glivec®, Gleevec™) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target: Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study. *Eur J Cancer* 2003, **39**, 2006–2011
2. Stroobants S, Goeminne J, Seegerts M, *et al*. ^{18}FDG-Positron emission tomography for the early production of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec®). *Eur J Cancer* 2003, **39**, 2012–2020.
3. Hirota S, Isozaki K, Moriyama Y, *et al*. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998, **279**, 577–580.
4. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI571, a selective tyrosine kinase inhibitor. *Blood* 2000, **96**, 925–932.
5. Tuveson DT, Fletcher CDM, Singer S, Jacks T, Fletcher JA, Demetri GD. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. *Oncogene* 2001, **20**, 5054–5058.
6. Joensuu H, Roberts PJ, Sarlomo-Rikala M, *et al*. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001, **344**, 1052–1056.
7. van Oosterom AT, Judson I, Verweij J, *et al*. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001, **358**, 1421–1423.
8. Demetri GD, von Mehren M, Blanke CD, *et al*. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002, **347**, 472–480.
9. Hanahan D, Weinberg R. The hallmarks of cancer. *Cell* 2000, **100**, 57–70.
10. Rubin BP, Schuetze SM, Eary JF, *et al*. Molecular targeting of platelet-derived growth factor B by imatinib mesylate in a patient with metastatic dermatofibrosarcoma protuberans. *Clin Oncol* 2002, **20**, 3586–3591.
11. Pietras K, Sjoblom T, Rubin K, Heldin CH, Ostman A. PDGF receptors as cancer drug targets. *Cancer Cell* 2003, **3**, 439–443.
12. Pietras K, Rubin K, Sjoblom T, *et al*. Inhibition of PDGF receptor signaling in tumor stroma enhances antitumor effect of chemotherapy. *Cancer Res* 2002, **62**, 5476–5484.