TOPIC

Imatinib – New Perspective in Tumor Treatment

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SUMMARY

The targeted inhibition of signal transduction is one of the novel approaches to anticancer therapy. The review outlines the recent experience with imatinib (Glivec), a potent inhibitor of the protein kinases bcr-abl, c-kit and platelet-derived growth factor receptor kinase. Due to inhibition of bcr-abl tyrosin kinase, imatinib has rapidly become the standard therapy for chronic myeloid leukemia. Inhibition of c-kit receptor explains why it is effective in the treatment of patients with metastatic gastrointestinal stromal tumors. Another known target of imatinib is tyrosinkinase of the receptor for platelet-derived growth factor (PDGFR), which is activated in various malignancies, particularly in dermatofibrosarcoma protuberans. Discovery of the novel fusion gene in hypereosinophilic syndrome (FIPILI-PDGFR-alpha, product of which is imatinib sensitive protein kinase) has allowed the use of imatinib for treatment of this disease. The possibility of combining imatinib and conventional chemotherapy or other key signal transduction inhibitors is mentioned.

Key words: imatinib, chronic myeloid leukemia, gastrointestinal stromal tumor, hypereosinophilic syndrome.

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One of the most interesting ways of influencing malignant proliferation is the inhibition of intracellular processes that participate in the transformation of the normal cells into tumor cells. The vast majority of experience available to date has been documented with the use of substances blocking the course of the signal transduction, e.g. the transmission of the signal from cellular receptors into cellular nucleus which influences the transcription and change of the cellular fenotype. Possible therapeutic targets are described in Figure 1 and have been indicated elsewhere (1). In addition to the substances blocking the cellular receptors to which particularly monoclonal antibodies are used, several inhibitors of receptor tyrosin kinases have been launched into the clinical practice. Those are mainly low-molecular substances blocking phosphorylation of these kinases due to which transduction cascade is inhibited. The inhibitors of receptors for EGF - gefitinib (Iressa) or erlotinib (Tarceva) are examples of these substances; the inhibitor of receptor kinase for VEGF (semaxanib) has been studied. Inhibitors of proteinkinases are usually low-molecular compositions, as Figure 2 describes.

The pathological oncogenic protein, a product of fusion gene originating after the reciprocal translocation of the distal part of the long branch of the chromosome 22 and chromosome 9 (t9:22) q34:q11 also has protein-kinase activity. The fusion gene, the Ph chromosome (Fig. 3) encodes pathological protein bcr-abl with protein-kinase activity responsible for the intensive proliferation of the myeloid precursors. The onset of chronic myeloid leukemia is the result of this process. Fusion protein has also further activities stimulating the proliferation, as described in Figure 4. These are activation of the transduction cascade ras, activation of the cascade jak/STAT, activation of the phospholipase way and increase of the concentration of radicals of oxygen (ROS).

Developed superoxides induce transcription factors, impair the stability of genoma and could contribute to malignant transformation of cell. ABD (actin binding protein) causes the phosphorylation of the focal adhesive proteins in the cytoskeleton, which can increase the oncogenic effects of protein bcr-abl (2). The protein bcr-abl influences also apoptosis, particularly by means of the activation of nuclear factor kappa-B, which is considered to be the significant antiapoptotic factor, in addition to various other functions (3–5).

Imatinib (Glivec) is a derivative of amidopyrimidine, originally named STI-571 (signal transduction inhibitor) and causing the blockage of bcr-abl tyrosinkinase and suppressing the proliferation of the cells activating bcr-abl, e.g. the first of all the cells with Ph chromosome. The structural formula is indicated in Figure 2. It became one of the most effective medications for the treatment of the chronic myeloid leukemia (6). The functional mechanism is based on the occupation of the binding place for ATP. Binding of ATP to bcr-abl tyrosinkinase is performed by phosphorylation of the tyrosine remnants from various substrates and following acceleration of the proliferation. Imatinib blocks this binding and decreases the proliferation activity in this way.

IMATINIB USE FOR BLOCKAGE OF PROTEIN-KINASE bcr-abl

Including imatinib in the treatment of chronic myeloid leukemia was greeted with enthusiasm because imatinib induces hematological remission in more than 90% of patients and also cytogenetic remission in 60–80% of patients (3). The highest percentage of cytogenetic remissions after imatinib has been described in recently diagnosed patients who have not yet been treated; however, very good results have also been noted in the cases of failure to respond to the standard therapy (usually interferon or interferon combined with chemotherapy). A slightly lower ratio of responses to imatinib has been observed in the accelerated phase, and uncertain results have been noted in blast crisis, when the results of imatinib therapy has not differed significantly from the results of conventional chemotherapy (7, 8). Imantinib therapy has usually been well tolerated; adverse effects have not been serious. The most frequent adverse effects were myalgia, arthralgia, muscular spasms, skin rash and nausea,

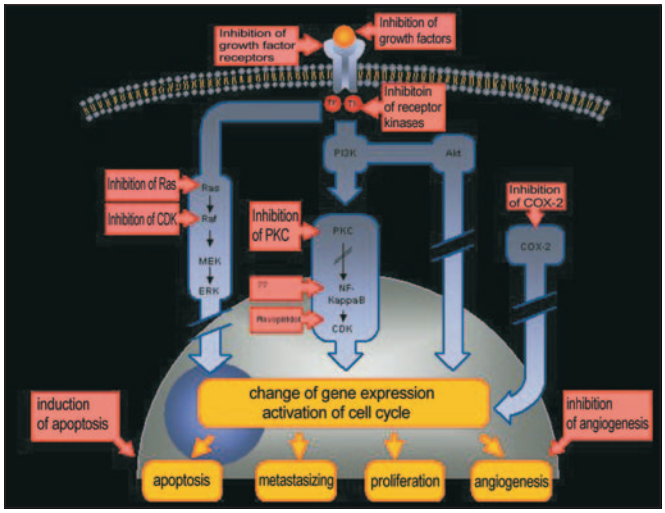

Fig. 1. Scheme of possible therapeutic targets in intracellular processes

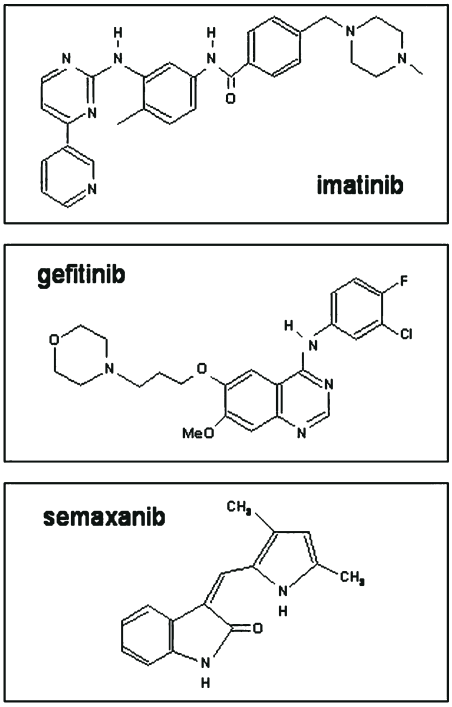

Fig. 2. Structural formulas of several proteinkinase inhibitors

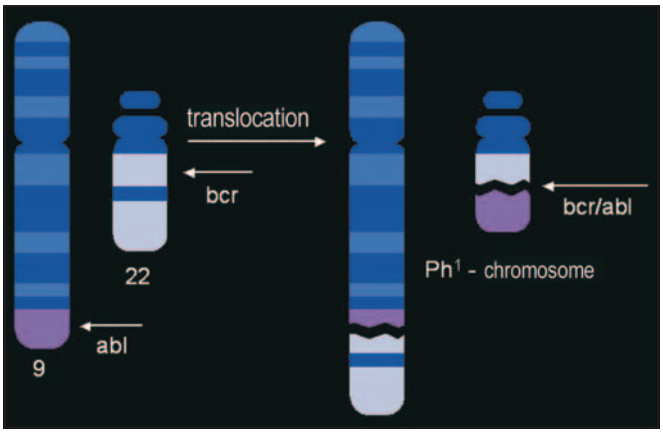

Fig. 3. Reciprocal translocation t(9:22) q 34:q 11 – origin of Ph chromosome

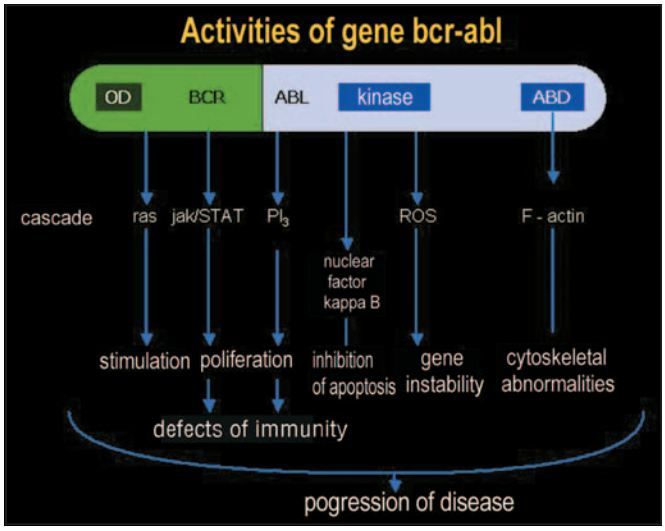

Fig. 4. Comprehension of the biological activity of the bcr-abl gene (OD= oligodimerisation domain, ABD= actin binding domain, ROS= reactive oxygen species)

rarely hepatotoxicity and retention of fluids. For previously treated patients granulocytopenia and thrombocytopenia has been described. Standard daily dose is 400 mg, long term treatment till loss of sensitivity. Progressive development of resistance to imatinib has been explained by activation of other mutagenic oncogenes during the clonal divergency, which had been developed progressively in course of CML. Higher impact of increased activity of glycoprotein P (by alteration of the gene for multiplex drug resistence – MDR) could not be excluded. A further possible cause of this is the increased activity of bcr-abl mutation in abl-kinine domain. Increased activity could be overtaken by dose escalation; however, aberrant mutation creates difficulties in binding imatinib to bcr-abl mutated cells. Then these mutated cells "overgrow" the cells with wild type of bcr-abl, sensitive to imatinib (9). Cytogenetic investigation (Ph+ cells) has been used for monitoring the response to imatinib, identification of cells transferring the fusion gene bcr-abl by FISH method , molecular biological investigation by real time polymerase chain reaction method (concentration of bcr--abl transcripts) (10).

The significance of the increased activity of the supressor gene WT-1 is also studied. Activity of that has decreased in correlation to a decrease of Ph+ cells (11). If the transcription of bcr-abl does not decrease during the 3 months imatinib treatment, the complete cytogenetic remission is not probable. In cases of imatinib resistance, a combination of that and cytarabin - or a switch to another treatment regimen – is recommended.

Some novel drugs have been tested, e.g. homoharringtonin, decitabin, or zebularin (12, 13). Another possibility, to date only experimentally studied, is the additive effect of imatinib contemporary administered with other transduction inhibitors. Particularly inhibitors of ras cascade the course of which is phenyltransferase dependent has been studied (14, 15). Two preparations of more than 20 farnesyltansferase inhibitors have been tested in the clinical trials, Tipifarnib (Zarnestra) and onafarnib (Sarasar) (16). There is a potential possibility of the contemporary administration of other intracellular inhibitors including the antiangiogenic preparations (17), as noted in Table 1.

Tab. 1. Inhibition effects of imatinib and possible clinical use

Target tyrosinkinase	Clinical use
bcr-abl	CML
c-kit	GIST, SCLC
PDGFr	dermatofibrosarcoma protuberans gliomas fibrosarcomas myeloproliferative sy?
FIPILI-PDGFr	hypereosinophilic syndroma chronic eosinophilic leukemia

CML – chronic myeloid leukemia, GIST – gastrointestinal stromal tumor, SCLC – small cell lung cancer

Tab. 2. Other possible intracellular inhibitors suitable for combination with imatinib

Farnesyltransferase inhibitors	onafarnib (Sarasar) tipifarnib (Zarnestra)
JAK/STAT cascade inhibitors	tyrfostin
fosfolipase inhibitors	wortmanin
apoptosis inductors	arsentrioxide
cdk inhibitors	geldanamycin
angiogenesis inhibitors?	semaxanib
proteasom inhibitors?	bortezomib (Velcade)

IMATINIB USE IN THE BLOCKAGE OF THE TYROSINKINASE RECEPTOR FOR SCF (STEM CELL FACTOR)

Imatinib also causes inhibition of other tyrosinkinases, what enables its possible therapeutic use not only in CML. It blocks e.g. tyrosinkinase receptor for SCF (stem cell factor, c-kit ligand), coded by protooncogene c-kit. An acquired mutation of c-kit gene and following induction of c-kit expressing cells proliferation had been found in relatively rare gastrointestinal tumor, resp. sarcoma (GIST) totally resistant to conventional chemotherapy and radiotherapy (18, 19). Radical surgery remains the primary treatment of GIST. The therapeutic efficacy of imatinib for metastatic forms has been proved (20). It also brings benefits in adjuvant therapy after surgery to achieve positive response or in neoadjuvant therapy directed to improve tumor operability (21). Increased expression of c-kit has also been found in some tumors of epithelium, e.g. small cell lung carcinoma (SCLC), in which clinical trials have also begun. Further tumors with increased c-kit expression are ovarial carcinoma and testicular carcinoma. Nevertheless, increased c-kit expression does not implicitly mean imatinib sensitivity, which should be conclusively proved by clinical research (22).

IMATINIB USE IN THE TYROSINKINASE RECEPTOR FOR PFGF BLOCKAGE

Another possible target for imatinib is tyrosinkinase receptor for platelet growth factor (PDGFr). This growth factor is a mitogene for the connective tissue, and its autocrinic stimulation is supposed to be significant in the pathogenesis of several tumors. The autocrinic PDGF activation has been described at dermatofibrosarcoma protuberans, in which the fusion gene originating after the chromosomal transformation between the 17 and 22 chromosomes triggers autocrinic stimulation (3). In this indication the clinical efficacy of imatinib had been described. It seems that imatinib inhibition of PDGFr could also influence other tumors such as other fibrosarcomas or prostatic carcinoma and particularly gliomas where autocrinic stimulation of c-kit plays a role in their pathogenesis. Imatinib use in the treatment of several myeloproliferations besides chronic myeloid leukemia has been considered (23).

IMATINIB USE IN BLOCKAGE OF THE TYROSINKINASE FIPILI-PDGFR-ALPHA

Recently a new fusion gene originating in interstitial deletion of chromosome 4q12 has been described, the product of which is imatinib sensitive tyrosinkinase FIPILI-PDGFr-alfa causing eosinophillic proliferation and the onset of idiopatic hypereosinophilic syndroma (24). Imatinib therapy induces complete remission in almost 95% of patients and is also effective in patients with chronic eosinophilic leukemia (25, 26).

CONCLUSION

Imatinib is the most effective treatment of chronic myeloid leukemia at the present time, though allogenic stem cell transplantation remains the only curative therapy (12, 23). However, it is accompanied by large peritransplant morbidity and mortality, and it has various limits (e.g. age, suitable donor). For many patients imatinib remains a suitable therapeutic alternative. It is the effective therapy not only in CML but also in gastrointestinal stromal tumors, and due to the inhibition effect on various types of tyrosinkinases it should not be excluded from possible future treatment regimens in other tumors as well.

Abbreviations

ABD – actin binding protein
ATP – adenosintriphosphate
EGF – epidermal growth factor
MDR – multiple drug resistence
PDGFR – platelet derived growth factor receptor
ROS – reactive oxygen species
SCF – stem cell factor
SCLC – small cell lung cancer
STI-571 – signal transduction inhibitor
VEGF – vascular endothelial growth factor

REFERENCES

1. **Klener, P.:** Protinádorová chemoterapie pro 21.století. Klin. Onkol., 2003, 16, pp. 243- 248.
2. **Sattler, M., Griffin, J. D.:** Molecular mechanisms of transformation by the bcr-abl oncogene. Semin. hematol., 2003, (Suppl. 2), pp. 4-10.
3. **Capdeville, R., Silberman, S.:** Imatinib: A targeted clinical drug development. Semin. Hematol, 2003, 40 (Suppl.2), pp. 13-20.
4. **Carg, A., Aggarwal, B. B.:** Nuclear transcription factor kappa B as a target for cancer drug development. Leukemia, 2002, 16, pp. 1053-1068.
5. **John, A. M., Thomas, S. B., Mufti, G. J. et al.:** Targeted therapies in myeloid leukemia. Semin. Cancer Biol., 2004, 14, pp. 41-63.
6. **Talpaz, M., Silver, R. T., Drucker, B. J. et al.:** Imatinib induces durable hematologic and cytogenetic response in patients with accelerated phase chronic myeloid leukemia. Results of a phase II study. Blood, 2002, 99, pp. 1928.
7. **Angstreich, G. R., Smith, B. D., Jones, R. J.:** Treatment options for chronic myeloid leukemia: imatinib versus interferon versus allogeneic transplant. Curr. Opin. Oncl., 2004, 16, pp. 95-99.
8. **Goldman, J. M.:** Chronic myeloid leukemia – still a few questions. Exp. Hematol. 2004, 32, pp. 2-10.
9. **Holtz, M. S., Bhatia, R.:** Effect of imatinib mesylate on chronic myelogenous leukemia hematopoietic progenitor cells. Leuk. Lymphoma, 2004, 45, pp. 237-245.

10. **Hochhaus, A.:** Cytogenetic and molecular mechanisms of resistance to imatinib. Semin. Hematol., 2003, 40 (Suppl. 2), pp. 69-70.
11. **Cilloni, D., Saglio, G.:** Usefulness of quantitative assessment of Wilms tumor suppressor gene expression in chronic myeloid leukemia patients undergoing imatinib therapy. Semin. Hematol. 2003, 40 (Suppl.2), pp. 37-41.
12. **Cheng, J. C., Matsen, C. B., Gonzales, F. A. et al.:** Inhibition of DNA methylation and reactivation of silence genes by zebularin. J. Natl. Cancer Inst., 2003, 05, pp. 399-409.
13. **Tipping, A. J., Mělo, J. V.:** Imatinib mesylate in combination with other chemotherapeutic drugs: in vitro studies. Semin. Hematol., 2003, 40 (Suppl. 2), pp. 83-91.
14. **Campbell, P. M., Der, J. C.:** Oncogenic ras and its role in tumor cell invasion and metastasis. Semin. Cancer biol., 2004, 114, pp. 105-114.
15. **Daley, G. Q.:** Toward combination target-directed chemotherapy for chronic myeloid leukemia: Role of farnesyl transferase inhibitors. Semin. Hematol., 40 (Suppl. 2), pp. 11-14.
16. **Lancet, J. E., Rosenblatt, J. D., Karp, J. E.:** Farnesyltransferase inhibitors and myeloid malignancies: Phase I evidence of Zarnestra activity in high risk leukemias. Semin. Hematol., 2002, 39, pp. 31-35.
17. **Rak, J.,Yu, J. L.:** Oncogenes and tumor angiogenesis. Semin. Cancer biol., 2004, 14, pp. 93-104.
18. **Croom, K. F., Perry, C. M.:** Imatinib mesylate in the treatment of gastrointestinal stromal tumours. Drugs, 2003, 63, pp. 523-524.
19. **Reichardt, P., Pink, D., Mrozek, A. et al.:** Gastrointestinal stromal tumors (GIST). Z. Gastroenterol., 2004, 42, pp. 327-341.
20. **Jager, P. L., Gietema, J. A., VanDerGraaf, W. T.:** Imatinib mesylate for the treatment of gastrointestinal stromal tumours: best monitored with FDG-PET. Nucl. Med. Commun., 2004, 25, pp. 433-438.
21. **Eisenberg, B. L., Judson, I.:** Surgery and imatinib in the management of gastrointestinal stromal tumors. Emerging approaches to adjuvanat and neoadjuvant therapy. Ann. Surg. Oncol., 2004, 11, pp. 465-475.
22. **Ramadori, G., Fuzesi, L., Grabbe, E. et al.:** Successful treatment of hepatocellular carcinoma with the tyrosine kinase inhibitor imatinib in a patient with liver cirrhosis. Anticancer Drugs, 2004, 15, pp. 405-409.
23. **Krystal, G. W.:** Imatinib mesylate (STI 571) for myeloid malignancies other than CML. Leuk. Res., 2004, 28 (Suppl. 1), pp. 53-59.
24. **Cools, J., DeAngelo, D. J., Gotlib, J. et al.:** A tyrosinkinase created by vision of the PDGFR-alpha and FIPILI genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N. Engl. J. Med., 2003, 348, pp. 1201-1214.
25. **Coutré, S., Gotlib, J.:** Targeted treatment of hypereosinophlic syndromes and chronic eosinophilic leukemia with imatinib mesylate. Semin. Cancer Biol., 2004, 14, pp. 23-31.
26. **Or, R., Shapira, M. Y., Resnick, I. et al.:** Nonmyeloablative allogeneic stem cell transplantation for the treatment of chronic myeloid leukemia in first chronic phase. Blood, 2003, 101, pp. 441-445.

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