The effect of Imatinib, in combination with 1,25(OH)2D3, Inhibitory and as Potential Immunomodulatory in Cancer and Autoimmunity Treatment and Prevention

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Abstract: Imatinib is highly active and has an acceptable level of toxicity when given alone for the treatment of chronic-phase CML and gastrointestinal stromal tumors. Not only as therapy, Imatinib also acted as a tool for understanding the mechanisms of the diseases like CML and GIST. Various studies are ongoing to explore its benefits in other cancers also.

Growing evidence indicates that the immune system has a major role both in determining the therapeutic efficacy of imatinib and in restraining the emergence of escape mutations.

Several studies demonstrated that Imatinib had beneficial effects on EAE by attenuation in the severity and a delay in the onset of disease. In vitro, imatinib inhibited cell proliferation, MMP-2 expression and activity and also attenuated the production of proinflammatory cytokines. Imatinib blocks proliferation and induces apoptosis of BCR-ABL-expression in CML. The tyrosine kinase inhibitors have proven to be well tolerated for long periods treatment, with minimal adverse events, in Cancer.

Vitamin D is a fat-soluble vitamin that plays an important role in bone metabolism and seems to have some anti-inflammatory and immune-modulating properties.

In addition to its role in calcium homeostasis, it is believed that the active form of vitamin D has immunomodulatory effects on cells of the immune system, particularly T lymphocytes, as well as on the production and action of several cytokines.

Current studies have linked the deficiency of vitamin D with different autoimmune diseases, including insulin-dependent diabetes mellitus (IDDM), multiple sclerosis (MS), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA).

In this article, I discuss the Development of imatinib, Clinical Pharmacology Imatinib, In vitro profile of imatinib and In vivo profile of imatinib: animal models. Moreover,Immunologic Functions of Vitamin D, Hormonal Function of Vitamin D, Cellular Proliferation and Differentiation and Vitamin D and Autoimmune Disease as well as , Mitoxantrone, in combination with 1,25(OH)2D3,, Inhibitory and Immunomodulatory, Potential in Cancer and Autoimmunity Immunotherapy in animal model

Key Word: Imatinib, 1, 25 (OH) 2D3, Inhibitory, Immunomodulatory, Animal Model, Cancer, and Autoimmunity

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1. Introduction

Deregulated protein tyrosine kinase activity is central to the pathogenesis of human cancers. Targeted therapy in the form of selective tyrosine kinase inhibitors (TKIs) has transformed the approach to management of various cancers and represents a therapeutic break through.

Previous studies demonstrated that, Imatinib was one of the first therapies to show the potential effect for various cancers. Studies evidenced that Imatinib, an oral targeted therapy, inhibits tyrosine kinases specifically BCR-ABL, c-KIT, and PDGFRA. Apart from its remarkable success in CML and GIST,

The active sites of tyrosine kinases each have a binding site for ATP. The enzymatic activity catalyzed by a tyrosine kinase is the transfer of the terminal phosphate from ATP to tyrosine residues on its substrates, a process known as protein tyrosine phosphorylation. Imatinib works by binding close to the ATP binding site, locking it in a closed or self-inhibited conformation, therefore inhibiting the enzyme activity of the protein semicompetitively(1).

This process ultimately results in “switching-off” the downstream signaling pathways that promote leukemogenesis. Imatinib also inhibits the ABL protein of noncancer cells, but cells normally have additional redundant tyrosine kinases which allow them to continueto function even if ABL tyrosine kinase is inhibited. Some tumor cells, however, have a dependence on BCR-ABL(2). Inhibition of the BCR-ABL tyrosine kinase also stimulates its entry into the nucleus, where it is unable to perform any of its normal antiapoptotic functions (3).

Vitamin D exists in several forms including 25-hydroxyvitamin D [25(OH)D], the primary circulating form, and 1,25-dihydroxyvitamin D [1,25(OH)2D], the active form (4). The classical actions of vitamin D are to promote calcium homeostasis and to promote bone health. Vitamin D enhances absorption of calcium in the small intestine and stimulatesosteoclast differentiation and calcium reabsorption of bone. Vitamin D additionallypromotes mineralization of the collagen matrix in bone.

These data show that 1,25-(OH)2D inhibits DC maturation and inhibits the induction of pro-inflammatory Th1 cells. In addition, the formation of tolerogenic T cells, an active mechanism for natural immune suppression, and the production of anti-inflammatory cytokine IL-10 are

promoted by 1,25-(OH)2D. 1,25-(OH)2D promoted the induction of (pro)monocytic differentiation to macrophages(5). 1,25-(OH)2D increases the antigen-presenting activity of macrophages and enhances the phagocytic activity of macrophages(6),(7).

2. Development of imatinib

Given the success of imatinib and the enormous interest in protein kinase inhibitors, it is easy to forget the degree of skepticism that kinase inhibitors faced from the scientific community and the pharmaceutical industry in the 1980s and 1990s. One area of skepticism was whether compounds with specificity amongst protein kinases could be developed. The other reflected the belief that targeting of a single molecular defect with a selective agent would not be sufficient to treat highly heterogeneous cancers. Despite this skepticism, bythe early 1990s, the 2-phenylaminopyrimidines were firstreported as kinase inhibitors with selectivity for the proteinkinase C (PKC), Abelson (ABL) and platelet-derivedgrowth factor receptor (PDGFR) kinases(8),(9),(10),(11),(12). As is the case with many drugs currently in clinical trials, an initial lead compound was identified by testing compound libraries for inhibition of protein kinases in vitro. The activity of the 2-phenylaminopyrimidine series was subsequently optimized for inhibition of ABL and PDGFR, by synthesizing a series of chemically related compounds and analyzing the relationship between their structure and activity in a variety of assays. An important finding was that methyl substitution of the anilino-phenyl ring at the 6-position led to potent inhibition of the ABL and PDGFR kinases, but abolished activity on the PKC family. The 2-phenylaminopyrimidine class was finally optimized for absorption, distribution, metabolism and excretion properties by the introduction of the *N*-methyl piperazine group. The most potent molecules in the series were inhibitors of both the ABL and the PDGFR kinases. Imatinib emerged from these efforts as the lead compound for preclinical development based on its selectivity against CML cells in vitro and its drug-like attributes, including pharmacokinetic and formulation properties. The in vitro screening employed a panel of isolated protein kinase enzyme assays for initial chemical optimization. Although this sounds simple now, this was not the case in the late 1980s, when methods for the recombinant expression of active tyrosine protein kinases were in their infancy (e.g. Foulkes et al. (13), and Lydon et al. (14). It was only with the development of baculovirus expression systems that enzymatically pure kinases with high specific activity could be obtained (15),(16),(17). Such high quality enzymes were essential for effective high throughput screening, inhibitor characterization, and chemical optimization of lead compounds.

3. Clinical Pharmacology

Tyrosine kinases are important mediators of the signaling cascade, determining key roles in diverse biological processes like growth, differentiation, metabolism, and apoptosis in response to external and internal stimuli. Deregulation of protein kinase activity has been shown to play a central role in the pathogenesis of human cancers. Imatinib, a 2-phenyl amino pyrimidine derivative, is a tyrosine kinase inhibitor with activity against ABL, BCR-ABL, PDGFRA, and c-KIT. The active sites of tyrosine kinases each have a binding site for ATP. The enzymatic activity catalyzed by a tyrosine kinase is the transfer of the terminal phosphate fromATP to tyrosine residues on its substrates, a process known as proteintyrosine phosphorylation. Imatinib works by binding close to the ATP binding site, locking it in a closed or self-inhibited conformation, therefore inhibiting the enzyme activity of the protein semicompetitively(1). This

process ultimately results in "switching-off" the downstream signaling pathways that promote leukemogenesis. Imatinib also inhibits the ABL protein of noncancer cells, but cells normally have additional redundant tyrosine kinases which allow them to continueto function even if ABL tyrosine kinase is inhibited. Some tumor cells, however, have a dependence on BCR-ABL (2). Inhibition of the BCR-ABL tyrosine kinase also stimulates its entry into the nucleus, where it is unable to performany of its normal antiapoptotic functions (18). Imatinib is well absorbed after oral administration with a bioavailability exceeding 90% (19). It is extensively metabolized, principally by cytochrome P450 (CYP)3A4 and CYP3A5, and can competitively inhibit the metabolism of drugs that are CYP3A4 or CYP3A5 substrates. Interactions may occur between Imatinib and inhibitors or inducers of these enzymes, leading to changes in the plasma concentration of Imatinib as well as coadministered Drugs (20). Imatinib is generally well tolerated. Common side effects include fluid retention, headache, diarrhea, loss of appetite, weakness, nausea and vomiting, abdominal distention, edema, rash, dizziness, and muscle cramps. Serious side effects may includemyelosuppression, heart failure, and liver function abnormalities (21).

2. In vitro profile of imatinib

Inhibition of kinase activity

Studies using purified enzymes expressed as bacterial fusion proteins or using immune-precipitations of intact proteins showed that imatinib potently inhibits all of the ABL tyrosine kinases. This includes cellular ABL, viral ABL (*v*-ABL), and BCR-ABL (8),(22),(23). In contrast, the compound was inactive against serine/ threonine kinases, did not inhibit the epidermal growth factor (EGF) receptor intracellular domain, and showed weak or no inhibition of the kinase activity of the receptors for vascular endothelial growth factor (VEGF-R1 and VEGF-R2), fibroblast growth factor receptor 1 (FGF-R1), tyrosine kinase with immunoglobulin and EGF homology-2 (TIE-2 [TEK]), c-MET, and nonreceptor tyrosine kinases of the SRC family (FGR, LYN, and LCK). The results of the kinase assays were confirmed in cell lines expressing constitutively active forms of ABL such as *v*-ABL (8), p210BCR-ABL (22), p185 BCR-ABL (24),(25), and translocatedets leukemia (TEL) ABL,(24), where imatinib was found to inhibit ABL kinase activity with 50% inhibitory concentration (IC50) values ranging between 0.1 and 0.35 M. Numerous Ph_ cell lines derived from patients with CML or acute lymphoblastic leukemi(8)a (ALL) have subsequently been tested. In most of these lines, the IC50 values were also in the range of 0.1 to 0.5 M, indicating that the compound effectively penetrates the cell membrane (25),(26),(27). Consistent with its in vitro profile, imatinib inhibited signaling of the ligand-activated platelet-derived growth factor receptor (PDGFR) (23),(11), as determined by ligand-stimulated PDGFR autophosphorylation, at an IC50 of 0.1 to 1 M. Inhibition of the constitutively active TEL-PDGFR fusion protein was observed at an IC50 of 0.15 M (24). Furthermore, the compound potently inhibited autophosphorylation of the KIT receptor upon binding of its cognate ligand, stem-cell factor (SCF), (23),(28), and to suppress KIT autophosphorylation in a cell line established from a patient with a gastrointestinal stromal tumor (GIST) with an activating Kit mutation (29). In contrast, signal transduction mediated by EGF, insulin, insulinlike growth factor I (IGF-I), FGF, and phorbol ester was insensitive to imatinib(8). Furthermore, imatinib did not affect FLT-3 or the receptor for colony-stimulating factor 1 (CSF-1, FMS), or the nonreceptor tyrosine kinases SRC and JAK-2.

3. In vivo profile of imatinib: animal models

To test the effects of imatinib on tumor growth, BCR-ABL– transformed 32D cells were injected into syngeneic mice.18 Oncedailyintraperitoneal treatment using doses of imatinib from 2.5 to 50 mg/kg, starting 1 week after cell injection, caused dosedependent inhibition of tumor growth, while 50 mg/kg intraperitoneal treatment was inactive against tumors derived from v-SRC–transformed 32D cells, consistent with the lack of inhibition of SRC kinase activity by imatinib. Similar experiments in nude mice using KU812 cells, a BCR-ABL_ human cell line, demonstrated the need for continuous inhibition of BCR-ABL kinase activity to achieve maximal antitumor effects (30). Early pharmacokinetic studies at Novartis had demonstrated that imatinib is rapidly absorbed following oral administration to mice and pharmacologically relevant concentrations are achieved in the plasma, with a half-life of approximately 1.3 hours. Optimization of the treatment schedule to 3 times daily administration of 50 mg/kg intraperitoneally or 160 mg/kg orally for 11 consecutive days, assuring continuous blockage of p210BCR-ABL tyrosine kinase, resulted in tumor-free survival of mice injected with KU812 cells.With the same schedule, established tumor nodules began to regress 48 hours after beginning treatment; by day 8, no treated animal had measurable disease. Eight of 12 animals remained tumor free with over 200 days of follow-up, while 4 relapsed on days 48 through 60. The antitumor effect of imatinib was specific for p210BCR-ABL expressing cells, as no growth inhibition occurred in mice injected with U937, a BCR-ABL_ myeloid cell line. Imatinib was also tested in the transduction-transplantation model of CML. In this system, lethally irradiated syngeneic mice receive marrow infected with a BCR-ABL retrovirus and consistently die within 3 weeks from an aggressive CML (31). Treatment with imatinib (50 mg/kg in the morning, 100 mg/kg in the evening) led to prolonged survival. Responses were quite variable, with 25% of animals having refractory disease. Imatinib was not capable of preventing CML, even if started as early as 48 hours after transplantation, but none of the responders progressed on therapy.
No consistent association between response and BCR-ABL Mrna and protein levels was seen, and no other cause underlying refractoriness could be determined. Notably, there was a trend toward “clonal depletion” in responding animals, suggesting that imatinib was able to successfully target some, but not all leukemic clones.

5. Activity in other tumors

According to the paradigm established above, imatinib would be expected to have activity against tumors where it has been established that a target of imatinib (i.e. ABL, ARG, KIT or PDGFRs) is critical to the pathogenesis of thecancer.The most striking example of this prediction being borneout has been the clinical results for imatinib in gastrointestinalstromal tumor (GIST). GISTs are mesenchymal neoplasmsthat can arise from any organ in the gastrointestinaltract or from the mesentery or omentum. More than 90% ofGISTs express KIT (32), and biochemical evidence of KITactivation can be found in almost all GISTs (33). In approximately90% of cases, this activation is linked to somaticmutations of KIT, usually involving exons 9 or 11 (33). Responserate of GISTs to single- or multi-agent chemotherapy is less than 5% (34). In contrast, in phase I and II trials of imatinib in GIST, 53–65% of patients had objective responses, using a minimum dose of 400 mg per day (35),(36). Translocations involving the *PDGFRB* gene have been identified in several myeloproliferative and myelodysplastic syndromes. The most common of these translocations, (q33;p13), is seen in a

subset of patients with chronic myelomonocytic leukemia (CMML) and results in fusion of the *EVT6* (*TEL*) and *PDGFRB* genes (37),(38). Several patients with CMML containing the (q33;p13) translocation have been treated with imatinib and all achieved complete hematologic remissions (39),(40). The PDGFRB pathway is also a target in dermatofibrosarcomaprotuberans (DFSP), a low-grade sarcoma of the dermis that often recurs after surgical excision. These tumors are characterized by a translocation involving the *COL1A1* and *PDGF-B* genes, which results in over-production of fusion COL1A1-PDGF-BB ligand and consequent hyperactivation of PDGFRB (41). It has been shown that imatinib inhibits the growth of DFSP cells both in culture and in immunodeficient Mice (42), and preliminary results in patients look promising (43),(44). The PDGF receptors and KIT are expressed in many common tumors and have been reported to be activated by both autocrine and paracrine mechanisms. However, it is unclear whether monotherapy with imatinib would be useful in any of these disorders. Imatinib may have a role in the treatment of such cancers, but meaningful conclusions will only be derived from carefully designed clinical trials that incorporate proteomic and genomic assessment of target activation status, with careful evaluation of responding patients. Thus far, there is one example where an empiric clinical trial of imatinib has shown remarkable success. Initial reports demonstrated that patients with hypereosinophilic syndrome (HES) achieved complete hematologic responses to single agent imatinib, often with relatively low doses (45). Molecular evaluations of these patients revealed an intrachromosomal deletion on chromosome 4 that fuses a gene of unknown function, *FIP1L1*, to the *PDGFRA*, resulting in activation of the PDGFRA (46). This fusion protein is likely the causative molecular abnormality of a subset of patients HES and accounts for the sensitivity to imatinib.

Immunologic Functions of Vitamin D

The expression of VDR in immunologic cells including antigen-presenting cells (APCs) and lymphocytes(47), as well as evidence of 1a-hydroxylase expression by activated macrophages12 suggests a role for vitamin D in the immune system. Vitamin D's effects specific to the innate immune system are mediated by transmembrane pathogen receptors that recognize cell membrane patterns from pathogenicorganisms called Toll-like receptors (TLRs) located in lymphopoietic cells, including Kupffer cellsand epithelial cells. Activation of these TLRs through cellular production of 1a-hydroxylase and VDR leading to 1,25(OH)2D3 synthesis results in synthesis of reactive oxygen species and antimicrobial peptides including cathelicidin in both macrophages and epithelial cells.(48). VDD may predispose individuals to endotoxin exposure secondary to decreased activation of this pathway. The clinical application of VDD in the antimicrobial response was shown by Liu et al.(48),who demonstrated human macrophage TLR activation led to expression of VDR and 1a-hydroxylase and thus cathelicidin,leading to death of intracellular Mycobacterium tuberculosis. Furthermore, African Americans, who havesignificantly decreased 1,25(OH)2D3 levels because of skin melanin content compared to Caucasian counterparts, were shown to have decreased production of cathelicidin. When vitamin D was repleted to physiologic levels, TLR-induced cathelicidin production was restored. Vitamin D also influences the adaptive immune system through modulation of both T and B lymphocytes as well as production of cytokines and immunoglobulins. Chen et al.(49), examined the role of vitamin D inregulation of autoantibody production and found that vitamin D inhibited proliferation of activated B cells, induced their apoptosis, and inhibited immunoglobulin secretion, suggesting that vitamin D-dependent Bcell regulation may be important in maintaining B-cell homeostasis. VDD may also contribute to B-cell hyperactivity.

Vitamin D acts on dendritic cells to reduce APC to CD4 cells, inhibit proliferation and differentiation of CD4 cells into T-helper1 (Th1) and Th17 cells, and promote differentiation into Th2 and Treg cells (50),(51). The decrease in Th1 cells leads to decreased production of interferon-gamma (IFN-c) and interleukin-2 (IL-2) as well as decreased macrophage activation, while the increase in TH2 cells leads to the production of IL-4, IL-5, and IL-10 (52). This association suggests that vitamin D tempers the adaptive immune response (53). Specific effects of vitamin D on liverrelated adaptive immunity remains to be determined but early evidence suggests that human T cells may be inactive against hepatitis C virus (HCV) infection in the setting of VDD (54).

Hormonal Function of Vitamin D

While the role of vitamin D in regulating bone homeostasis is well characterized, its role in the regulationof other hormones that are important in NAFLD, such as insulin and adiponectin, is less well defined.
The potential association between vitamin D and diabetes was first described by Campbell et al.(55) who noted glycemic control was worse in the winter months in 12 patients living in the Antarctic when the prevalence of VDD was higher. A subsequent systematic review of vitamin D and type 2 diabetes mellitus (DM) identified several longitudinal, observational studies reporting an inverse association between vitamin D status and risk of developing DM (56). Analysis of randomized controlled trials (RCTs) revealed no benefit from vitamin D supplementation in patients with normal glucose tolerance, but did show an improvement in glycemic indices in patients with baseline glucose intolerance or insulin resistance (IR). Mechanistically, vitamin D is thought to act on pancreatic b cells, which have been shown to contain the both VDR (57), and 1a-hydroxylase (58). Furthermore, the human insulin gene has been shown to contain a VDRE in its promoter region (59), as well as transcriptional activation through vitamin D ligand-dependent binding (60). Data suggest an association between vitamin D and adiponectin expression. A recent study demonstrated vitamin D supplementation with or without calcium was associated with an increase in serum adiponectin(61). Similarly, another study demonstrated an association between VDD and low adiponectin in type 2 diabetics(62). A potential explanation pertains to the renin-angiotensin system (RAS), where vitamin D decreases the expression of renin leading to decreased activation of the RAS(63). Adipocytes are known to stimulate a "local" RAS, which leads to inhibition of adiponectin secretion(64). Increased adipose-tissue RAS activation can therefore explain the low adiponectin levels seen with obesity, and conversely, vitamin D's inhibitory effects on the RAS can increase adiponectin levels.

Cellular Proliferation and Differentiation

Vitamin D also has effects on cellular proliferation and differentiation, predominantly in epidermal tissuesand in the setting of malignancy. Vitamin D has been shown to promote differentiation of keratinocytes and inhibit their proliferation.(65).Similarly, vitamin D has been shown to be involved in several malignancies where multiple neoplasms express the VDR.In keratinocytes with DNA damage, vitamin D promotes the repair of DNA damage, reduces apoptosis, and increases cell survival(66).A 4-year prospective trial suggested a clinical benefit

of vitamin D therapy where treatment with 1,100 IU vitamin D and 1,400-1,500 mg calcium daily showed a 77% reduction in certain malignancies, including breast and colon cancer. Unfortunately, the benefit of vitamin D does not appear to extend to treating cancer, although study has been limited to small case series. Further studies are needed to determine if the antineoplastic effects of vitamin D are clinically relevant.

Vitamin D and Autoimmune Disease

Diseases including multiple sclerosis (MS), rheumatoid arthritis (RA), diabetes mellitus (DM), inflammatory bowel disease and systemic lupus erythematosus (SLE) (reviewed in Reference (67). Reports of low serum vitamin D predicting development of autoimmune disease in the future have been published for MS, autoimmune DM and RA (68),(69),(70).There is also data linking decreased in utero exposure to vitamin D and islet cell autoimmunity (71). Lower in utero exposure assessed by a lower maternal intake of vitamin D during pregnancy in women whose prospective child was at risk of developing autoimmune DM is associated with a statistically increased risk of the child developing pancreatic autoimmunity.Vitamin D has also been shown to facilitate progression of existing autoimmune disease. Inone study, 161 patients with an early undifferentiated connective tissue disease werefollowed for a mean of over 2 years(72).Most patients did not progress and remained in anundifferentiated state. Thirty-five (21%) patients went on to develop a definedrheumatologic diagnosis including RA, SLE, Mixed Connective Tissue Disease, andSjogren's Disease while 126 did not progress. Baseline characteristics of the two groupswere similar. Importantly, the mean vitamin D level was significantly lower in the group
that progressed to a definitive disease. There have been many studies of vitamin D status in lupus patients from across the globe (73). Vitamin D levels are typically lower in patients than in disease or normal controls. Deficiency of vitamin D is extremely common, often with more than 50% of lupus patients with deficient levels and severe deficiency (vitamin D levels less than 10ng/ml) is not uncommon. Disease activity has been shown to correlate inversely with vitamin D in many but not all studies. Similar correlations between low levels of vitamin D and disease
activity and severity have been observed in other autoimmune diseases such as MS and RA (74),(75),(76),(77).

Conclusion

The tyrosine kinase (TK) inhibitor, Imatinib, has revolutionized the therapy of malignancies that are addicted to one of its target kinases, c-ABL, c-KIT, and PDGFR.

Imatinibmesylate is a selective protein tyrosine kinase inhibitor with immunomodulatory properties that abrogates multiple signal transduction pathways in immune cells.

Studies reported that, Imatinib is one of the most recent medications used for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST). It is an orally administered protein-tyrosine kinase inhibitor, an enzyme which is produced by BCR-ABL

fusion which results from translocation of 9:22 chromosome (Philadelphia chromosome). Imatinib blocks proliferation and induces apoptosis of BCR-ABL-expression in CML.

Recent studies have demonstrated a potential physiological role for vitamin D in regulating normal innate and adaptive immunity.

the increasing amount of data linking inadequate vitamin D levels to immune anomalies, such as increased infection rates and autoimmunity, is of great concern. On the basis of their widespread immunomodulatory actions, VDRagonists, and especially hypocalcemic vitamin D analogs,are plausible candidates for the prevention and/or treatment of infections such as tuberculosis and several autoimmune disorders.

Alternatively, as optimal functioning of the vitamin D autocrine and/or paracrine circuit crucially depends on adequate vitamin D levels,

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