

## Three Paths to Better Tyrosine Kinase Inhibition Behind the Blood-Brain Barrier in Treating Chronic Myelogenous Leukemia and Glioblastoma with Imatinib

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### Abstract

Chronic myelogenous leukemia (CML) can be controlled for years with the tyrosine kinase inhibitor imatinib but because imatinib poorly penetrates the blood-brain barrier (BBB), on occasion, the CML clone will thrive and evolve to an accelerated phase in the resulting imatinib sanctuary within the central nervous system. In this, CML resembles glioblastoma in that imatinib, which otherwise may be effective, cannot get to the tumor. Although a common street drug of abuse, methamphetamine is Food and Drug Administration–approved and marketed as a pharmaceutical drug to treat attention-deficit disorders. It has shown the ability to open the BBB in rodents. We have some clinical hints that it may do so in humans as well. This short note presents three new points potentially leading to better tyrosine kinase inhibition behind the BBB: 1) Pharmaceutical methamphetamine may have a useful role in treating both CML and glioblastoma by allowing higher imatinib concentrations behind the BBB. 2) The old antidepressant and monoamine oxidase inhibitor selegiline, used to treat Parkinson disease, is catabolized to methamphetamine. Selegiline, as a non-scheduled drug, may therefore be an easier way to open the BBB, allowing more effective chemotherapy with tyrosine kinases. 3) Dasatinib is a tyrosine kinase inhibitor with a spectrum of inhibition only partially overlapping that of imatinib and a mechanism of tyrosine kinase inhibition that is different from that of imatinib. The two should be additive. In addition, dasatinib crosses the BBB poorly, and it can therefore be expected to benefit from methamphetamine-assisted entry.

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### Prelude

“The battle is fought and decided by the quartermasters before the shooting begins,” said Erwin Rommel, Nazi general who won many smaller battles against much superior forces but ultimately lost all his bigger battles by his opponents’ superior quartermasters. The quartermaster corps supplies the tools and equipment of war to the combat troops—ammunition, food, fuel, transport, and weapons.

### Introduction

Isobe et al. [1] showed the consequences of chronic myelogenous leukemia (CML) of imatinib’s poor penetration of the blood-brain barrier (BBB). They reported a patient with CML with blast crisis limited to the central nervous system (CNS) compartment reminiscent of similar reports of CNS blast crisis occurring in otherwise well-treated patients on imatinib [2] or the situation seen occasionally in acute lymphoblastic leukemia [3] where the systemic malignant clone seems absent or pro-

foundly suppressed by imatinib yet the neoplasm reappears in the CNS. This is understandable because the cerebrospinal fluid (CSF) concentration of imatinib is less than 3% that of plasma in patients [1,3–5] and mice [6]. The retention of a malignant CML clone protected from exposure to imatinib behind the BBB, growing and evolving most dangerously even in the systemic presence of a safe and potent drug that would otherwise suppress it, parallels our predicament in glioblastoma where the cells start and finish their life course behind the BBB.

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Therefore, prognosis remains unusually poor. We require a better quartermaster corps than we now have to win that big battle, too.

The recent article by Isobe et al. [1] points out the problem in the context of CML that glioblastoma researchers have been wrestling with for decades [5,7–9]. In this short note, the rationale is discussed for using two currently marketed drugs with significant potential to open the BBB allowing better entry of tyrosine kinases (TKs) and therefore more effective treatment of both CML with CNS involvement and glioblastoma.

### Glioblastomas and TKs

Imatinib has shown good potential for anti-glioblastoma activity [10–15], but the problem, as for the patient of Isobe et al., has always been how to get adequate imatinib levels across the BBB to the malignant tissue [5,7,8].

Flow cytometry and immunohistochemistry show ample glioblastoma expression of TK targets [16–18], particularly so in the stem cell subpopulation [16–18], which should be susceptible to inhibition by imatinib if we could get the drug in adequate amounts across the BBB to the far-flung paucicellular extensions that remain after primary surgical resection. *In vitro* imatinib activity is good with growth arrest at 1 to 10  $\mu\text{M}$  and cytotoxicity at 20  $\mu\text{M}$  against glioblastoma cell lines [18].

Although glioblastoma are commonly said to have leaky BBBs, this is true only for the main tumor mass and then only parts of it. The far-flung microscopic extensions have intact BBBs [7,8].

The TK's activities in malignancy promotion in glioblastoma [19–21] are less clear, less well identified than the TK's overactivity in CML [22–24], but Src overactivity is one of them. Dasatinib is a good inhibitor of the specific TK BCR-ABL of CML, is clinically effective in CML [25–27], and is a much more potent inhibitor of Src than is imatinib [21,28,29].

### Opening the BBB

Having free access to CSF and glioblastoma tissue and the normal brain tissue surrounding the fine, microscopic extensions will greatly advance our ability to treat both CML and glioblastoma.

Although only documented in rodents, methamphetamine has the unusual attribute of massively disrupting the BBB for several hours (reviewed in Kast [30,31]). First synthesized in Japan in 1893, and although a common current drug of abuse [32,33], methamphetamine is a registered and marketed pharmaceutical drug in the USA and elsewhere (Desoxyn, Ovation Pharmaceuticals, recently purchased by Lundbeck Pharmaceuticals) and approved to treat attention-deficit problems in people older than 12 years (full prescribing information at <http://www.lundbeckinc.com/USA/products/CNS/desoxyn>). It is also approved for weight loss in women in the United States. Clinical experience suggests that it does not work for weight loss but does work well for relieving attention or concentration problems. For obvious reasons, it should not be used for either indication.

Patients report feeling no different on pharmaceutically prescribed methamphetamine than they do on the more commonly used methylphenidate (Ritalin, Concerta, and other brand names) or dexamphetamine (dextroamphetamine, Adderal, and other brand names).

Pharmaceutical methamphetamine has a circulating half-life of 9 to 15 hours,  $C_{\text{max}}$  of 1 hour, and a US Food and Drug Administration–approved maximum daily dose of 25 mg. Metabolism is hepatic; excretion is renal [33].

Given that rodent studies show that 64-kDa albumin can leak after methamphetamine treatment, we might expect imatinib, 494 Da, to do so [30,31].

We also have indirect evidence that abuse of street methamphetamine leads to BBB opening. Street methamphetamine users have a higher incidence of hepatitis C encephalitis than hepatitis C virus–infected nonusers [34] and higher CNS human immunodeficiency virus titer [35] indicating loss of BBB integrity.

### Indirect Methamphetamine Delivery

The monoamine oxidase inhibitor selegiline is approved, marketed, and used in many countries for treatment of depression (at higher doses) and Parkinson disease (at low doses). Relevant here is that selegiline's primary metabolite is methamphetamine [36–38]. Clinically significant amounts of methamphetamine are circulating in patients currently treated with selegiline [37,38]. Is that level enough to decrease BBB integrity? This matter requires urgent study. If selegiline-derived methamphetamine is disrupting BBB to any significant degree, then selegiline use must stop for all indications except potentially that of opening the BBB to allow more effective chemotherapy for CNS-resident malignancies. Because it is probable that selegiline catabolism to methamphetamine is primarily mediated by P450 2B6 [33], inducers of 2B6 such as pentobarbital, phenobarbital, or rifampin may enhance this process.

It may be parenthetically noted here that pentobarbital, a drug available worldwide since the 1950s, showed *in vitro* evidence of anti-glioblastoma effects seemingly independent of any selegiline exposure [39].

Selegiline and methamphetamine are both chiral molecules and, as such, have a complicated pharmacology. Dextro and levo enantiomers have different pharmacological attributes. If both or only one methamphetamine enantiomer opens, the BBB is unknown.

### Imatinib + Dasatinib Cooperation

In principle, dasatinib should be additive to some degree with imatinib on three accounts:

- (a) Although they are both called TKs, dasatinib and imatinib work by different and independent mechanisms. Imatinib binds to the ATP binding site of susceptible TKs, preventing required donation of the high-energy phosphate. Dasatinib binds to tyrosine-containing peptide's recognition site on TK, preventing target peptide binding and any consequent tyrosine phosphorylation. Dasatinib also penetrates the BBB poorly, achieving about a tenth of the CSF concentration compared with that of plasma [25] and may well benefit from methamphetamine-assisted CNS entry as well.
 

If methamphetamine indeed can provide us with free daily access to the brain tissue, then Src dephosphorylation (deactivation) becomes possible, too [31], to augment Src inhibition by dasatinib.
- (b) The arrays of different TKs that are inhibited by each are different. Although this may not be as important for CML where there is one prominent TK, the BCR-ABL TK, it seems that there are several overactive TKs in glioblastoma and multiple paths to activating each, so a net casted more broadly would be potentially useful. We have several preclinical experimental indicators that dasatinib-inhibited TKs are important in glioblastoma growth, prominent among them is Src [19,20,25]. Src can and does activate epidermal growth factor receptor in the absence of the epidermal growth factor [31], and this transactivation is an important element-enhancing growth in more than half of the glioblastomas [40].
- (c) Because the two have different mechanisms by which they inhibit TK, dasatinib/imatinib cross-resistance would be expected to develop more slowly [27,41].

It is currently unknown if there would be steric hindrance at any given TK between dasatinib and imatinib.

## Conclusions

Given glioblastoma's reliably fatal outcome within several years of diagnosis, and that 1 year after diagnosis, half of all patients are dead, BBB opening to allow higher imatinib brain tissue levels in addition to current treatments might be rewarding. After CNS relapse, CML patients may likewise benefit from methamphetamine-assisted opening of the BBB to allow better TK inhibition and more effective treatment.

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