Letter to the Editor

Essential Requirement for PP2A Inhibition by the Oncogenic Receptor c-KIT Suggests PP2A Reactivation as a Strategy to Treat c-KIT+ Cancers — Response

Kathryn G. Roberts, Fiona McDougall, and Nicole M. Verrills

We appreciate the letter by Dumont and colleagues, which confirms our recently published findings (1) on the potential efficacy of targeting protein phosphatase 2A (PP2A) activation by FTY720 for mutant c-KIT tumors. We also agree that consideration of the likely doses of FTY720 required for future human trials must be taken.

Both studies found the IC₅₀ of FTY720 for cell lines expressing mutant c-KIT to be in the low μmol/L range. The dose approved by the Food and Drug Administration (FDA) for use of FTY720 in multiple sclerosis (MS) patients is 0.5 mg/d, and while the average steady state levels of FTY720 in the phase III MS trials were in the low ng/mL range, it should be noted that (i) earlier trials for renal transplant patients tested higher doses for shorter periods and revealed no adverse effects at 2.5 mg/d for 3 months or 5 mg/d for 7 days (2, 3); and (ii) FTY720, and its metabolite FTY720-P, accumulates in the body, with ratios of plasma to target tissue of at least 1:10, in particular in lymphoid tissue (4). Thus, continued daily treatment as required for MS patients is likely to result in higher accumulated concentrations of FTY720 over time than those which would be anticipated from short-term treatments likely to be used for anticancer therapy. We would, therefore, predict that higher short-term doses of FTY720 are likely achievable, although clearly need to be tested in appropriate clinical trials.

In addition, we showed significant antitumor effects in a syngeneic mouse model of imatinib-resistant D816V c-KIT mutant myeloid cells at 10 mg/kg/d FTY720 for 3 weeks (1). Importantly, no toxic side effects were observed at this dose. Humans metabolize FTY720 far slower than rodents, with the half-life for FTY720 in humans at least 12 to 18 times longer than for rodents (2, 3, 5). Thus, relatively lower doses of FTY720 in humans than in mice should remain efficacious.

In vivo, FTY720 is phosphorylated to FTY720-P which binds to sphingosine 1-phosphate receptors, leading to modulation of chemotactic responses and lymphocyte trafficking. However, we and others have shown that the antileukemia effect of FTY720 is independent of its effects on sphingosine signalling, but rather is due to is activation of the tumor suppressor, PP2A (1). Thus, future studies investigating novel PP2A activating agents, without the immunosuppressive effects of FTY720, are clearly warranted.

In summary, the study by Dumont and colleagues confirms our findings that activation of PP2A by FTY720 is a promising approach for patients with mutant c-KIT cancers such as gastrointestinal stromal tumor (GIST), acute myelogenous leukemia (AML), and systemic mastocytosis, and we hope that future clinical trials for FTY720 will take into careful consideration the likely doses required for clinical efficacy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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