might do better if treated with a tyrosine kinase inhibitor that does not rely on OCT1 transporter activity. Functional OCT1 activity was determined by subtracting the uptake in the presence of amantadine, a specific OCT1 inhibitor according to the authors, from the uptake observed in unmanipulated cells. Examination of the data presented in their Figure 2 suggest that the IUR of imatinib in the absence of 500 μM of amantadine was increased by ~50% in OCT1-transfected KCL22 cells compared with mock-transfected cells.9 It was assumed that this difference in imatinib uptake could be attributed to OCT1 activity. Remarkably, although mock-transfected KCL22sumed that this difference in imatinib uptake could be attributed of OCT1 resulted in a limited (human embryonal kidney) cells, we show that overexpression demonstrate OCT1-mediated uptake of imatinib. Using HEK293demonstrate OCT1-mediated uptake of imatinib. Using HEK293/Neoobservations and our experimental data (see below), we argue that these inhibitor-based assays, designed to quantify functional OCT1 transporter activity, are in fact measuring additional, as yet unidentified, processes involved in imatinib IUR. Therefore, we have serious concerns about the use of “specific” OCT1 inhibitors to demonstrate OCT1-mediated uptake of imatinib. Using HEK293 (human embryonal kidney) cells, we show that overexpression of OCT1 resulted in a limited (~25%) increase in imatinib IUR (Figure 1A-C). These results coincide with other imatinib uptake studies using OCT1-transfected leukemic cells or oocytes.2,10 Furthermore, we show a dose-dependent decrease of imatinib uptake by amantadine in HEK293/OCT1 cells, but importantly, amantadine also decreased the imatinib uptake in HEK293/Neo control cells having an almost 4-log lower OCT1 expression (Figure 1D-E). Similar, even more profound results were obtained with prazosin (Figure 1F-G). Analogous inhibitory effects were also seen in the leukemic K562 cell line (Figure 1H-I). Importantly, both amantadine and prazosin decreased the IUR of imatinib independent of OCT1 expression levels.

In conclusion, we demonstrated that these inhibitors are not exclusively specific for OCT1 and, therefore, we would like to emphasize to be very cautious in the interpretation of inhibitor-based OCT1 data. In fact, our data indicate that prazosin and amantadine may also interfere with other imatinib uptake processes evidently distinct from that of OCT1-mediated IUR.

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To the editor:

Successful stem cell transplant with antibody-based conditioning for XIAP deficiency with refractory hemophagocytic lymphohistiocytosis

Marsh et al1 summarize the international experience of stem cell transplantation for X-linked inhibitor of apoptosis protein (XIAP) deficiency. They demonstrate a poor outcome for patients with active hemophagocytic lymphohistiocytosis (HLH) entering transplant (no survivors) and high transplant-related mortality with both myeloablative (7 of 8 patients) and reduced-intensity conditioning.
who was successfully transplanted using a monoclonal antibody
disease prophylaxis consisted of methylprednisolone (1 mg/kg/d),
splenomegaly, and increased ferritin [6500
0.1 mg/kg/d, his HLH remained refractory (ongoing pyrexias, hepato-
(CD34
College of Medicine). Peripheral blood was the stem cell source
provided from existing stocks by Malcolm Brenner, Baylor
monoclonal antibodies (not currently commercially available;
with alemtuzumab,
planted from a 10/10 matched unrelated donor using conditioning

Figure 1. Clinical course of XIAP-deficient patient with active
HLH treated with antibody-based minimal-intensity condi-
tioned stem cell transplant. Time course of conditioning, immu-
osuppression, neutrophil engraftment, donor chimerism, fevers,
and significant complications during the first 140 days following
stem cell transplant are shown. Total doses of conditioning drugs
were as follows: alemtuzumab, 1 mg/kg; fludarabine, 150 mg/m2;
cyclophosphamide, 1 g/m2; anti-CD45 monoclonal antibodies,
1600 µg/kg each of YTH24/54 antibodies; and etoposide, 150 mg/m2.
AV, adenoviremia requiring treatment with cidofovir; HSV, herpes
simplex virus stomatitis and viremia; mAbs, monoclonal antibodies;
PO, pulmonary edema as part of a capillary leak syndrome
requiring ventilatory support; Sk2, grade 2 skin graft-versus-host
disease treated by increased prednisolone dose; syn, syndrome.

(5 of 11 patients). This sensitivity to chemotherapy is predicted by
the cellular function of XIAP in regulating apoptosis in hepatocytes.\(^7\),\(^3\) There is thus a pressing need for transplantation protocols
associated with reduced toxicity in this condition. We reasoned that
minimal-intensity conditioning using monoclonal antibodies specifi-
cally targeting hematopoietic cells might enable engraftment with-
out toxicity to nonhematopoietic tissues. Here we present the first
case of a child with XIAP deficiency and treatment-resistant HLH
who was successfully transplanted using a monoclonal antibody-

A 2-year-old child presented with hepatosplenomegaly, pancy-
topenia, and culture-negative fevers. He progressed to profound
HLH associated with multigorgan failure. XIAP deficiency was
diagnosed by identifying reduced protein expression and a c.680G>A
mutation. He tolerated treatment with the HLH-2004 protocol
poorly, developing neurotoxicity (ciclosporin induced posterior
reversible encephalopathy), prolonged bone marrow suppression,
and infectious complications (Candida and bacterial sepsis, herpes
simplex virus stomatitis, parainfluenza II infection).

Immediately prior to transplantation, despite immunosuppression
with twice weekly etoposide at 150 mg/m² and dexamethasone at
0.1 mg/kg/d, his HLH remained refractory (ongoing pyrexias, hepatos-
pplenomegaly, and increased ferritin [6500 µg/L] and triglycerides
[2.57 mmol/L]), although his cytopenias responded. He was trans-
planted from a 10/10 matched unrelated donor using conditioning
with alemtuzumab, fludarabine, cyclophosphamide, and anti-CD45
monoclonal antibodies (not currently commercially available;
provided from existing stocks by Malcolm Brenner, Baylor
College of Medicine). Peripheral blood was the stem cell source
(CD34\(^+\) 20.5 \times 10^9/kg, CD3\(^+\) 4.0 \times 10^9/kg). Graft-versus-host
disease prophylaxis consisted of methylprednisolone (1 mg/kg/d),
micophenolate mofetil, and sirolimus. The patient was treated off-
study on a clinical governance basis.

Conditioning was well tolerated with no grade \(>2\) toxicities.
His main transplant complication was a syndrome of high fevers
(\(>40.5°C\)), associated with widespread rash, cardiovascular instability,
coagulopathy, and increasing hepatosplenomegaly (Figure 1).
These symptoms were contemporaneous with neutrophil recovery,
and he was initially treated for presumed engraftment syndrome
with 4 mg/kg methylprednisolone. Unfortunately, his symptoms
progressed, with development of a capillary leak syndrome associ-
ated with pulmonary edema requiring ventilation. His clinical
condition and mixed donor chimerism suggested relapsed HLH,
and he was treated with a single dose of etoposide. Upon converting
to 100% donor chimerism (day 45 + posttransplant) his symptoms
and organomegaly resolved. Other complications are summarized in
Figure 1. At 400 days posttransplant, he is no longer receiving im-
munosuppression drugs and has no evidence of HLH. Engraftment
studies show 100% donor hematopoiesis in all lineages, with good
immune reconstitution.

Here we demonstrate that, by combining a minimal-intensity
immunoablative conditioning regimen with a high stem-cell and
T-cell dose graft, XIAP deficiency with uncontrolled HLH can be
cured, even in the presence of other independent poor prognostic
factors. Although anti-CD45 monoclonal antibodies are not currently
commercially available, this case provides proof of principle that
antibody-based conditioning can secure curative engraftment
with low toxicity for patients with XIAP deficiency and refractory HLH
whose prognosis is otherwise extremely poor.\(^1\),\(^5\)

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References

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