Response

Role of TRAIL in osteoclastogenesis

In their letter, Labrinidis and colleagues raise the important issue of what (if any) might be the role of tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) in osteoclastogenesis. In previous studies, we[1,2] and 2 other independent groups of investigators[3-5] have shown that histidine-tagged (His-tag) recombinant TRAIL negatively regulates osteoclastogenesis by inhibiting preosteoclast differentiation and by inducing apoptosis of mature osteoclasts. On the other hand, Labrinidis et al were unable to confirm these previous findings when exposing osteoclastic cultures to the version of Apo2L/TRAIL that is currently being used in phase 1b clinical trials. Although Labrinidis et al emphasize the differences between the recombinant TRAIL preparations used in their and previous studies,[1-5] the possibility that the antiosteoclastic activity of TRAIL merely reflects an aspecific toxic effect of recombinant His-tag TRAIL is ruled out by 2 major considerations: (1) different groups of investigators have clearly documented the ability of recombinant His-TRAIL to induce in vitro prosurvival and even proliferative responses in a cell-type specific manner[6]; and (2) Roux's group has recently demonstrated that native TRAIL, produced and released in vitro by end-stage osteoclasts, promotes osteoclastic apoptosis through autocrine/paracrine mechanism.[4] Thus, besides blocking receptor-activator of NF-κB ligand (RANKL)–mediated osteoclastogenesis, osteoprotegerin (OPG) seems also able to protect mature osteoclasts from apoptosis mediated by native TRAIL endogenously produced by osteoclasts.[4] These findings corroborate the hypothesis that the relative concentrations of RANKL, OPG, and TRAIL at the local bone marrow level are critical for determining the fate of osteoclasts.[6,7] The net effect of TRAIL on osteoclastic differentiation and survival likely depends on the network of prosurvival and proapoptotic signals operating at a given time in the bone marrow microenvironment. In this respect, it should be considered that the antiosteoclastic activity of TRAIL reported by our and other groups[1-5] was observed in culture conditions in which purified populations of preosteoclasts were induced to differentiate along the osteoclastic lineage by adding recombinant macrophage–colony stimulating factor (M-CSF) plus RANKL to the culture medium. On the other hand, Labrinidis et al have cultured peripheral blood mononuclear cells (used as a source of preosteoclasts) in the presence also of vitamin D3 and dexamethasone, which are known to potently promote osteclastic survival and differentiation.[8] Thus, in our view, the novel contribution of the findings of Labrinidis et al with respect to previous data[1-5] relies on the demonstration that the presence in culture of vitamin D3 and dexamethasone abrogates the antidifferentiative and proapoptotic activities of TRAIL. However, this does not exclude a role of TRAIL in osteoclastogenesis, as suspected by Labrinidis et al, but rather suggests a level of molecular control on the antiosteoclastic activity of TRAIL. To verify our interpretation about the findings of Labrinidis et al, it will be important to analyze whether vitamin D3 and dexamethasone induce changes in the surface expression level of "death receptors" TRAIL-R1 and TRAIL-R2 and/or act at the level of intracellular critical determinants.

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To the editor:

Imatinib mesylate for platelet-derived growth factor receptor-beta–positive Erdheim-Chester histiocytosis

Erdheim-Chester disease (ECD) is a non-Langerhans form of $CD68^+$ $CD1a^-$ histiocytosis.[1-4] Interferon α (IFNα) is effective in ECD.[3,5] Efficacy is however depending on the site of involvement. Central nervous system (CNS) and cardiovascular involvement do not respond to IFNα and have a poor prognosis.[5]

Two patients suffering from Langerhans cell histiocytosis (LCH) and Rosai-Dorfman disease histiocytosis (RDD) were dramatically improved with imatinib mesylate (IM), a tyrosine kinase inhibitor, which selectively inhibits bcr-abl, KIT and platelet-derived growth factor (PDGF).[6,7] IM, initially given at 100 mg/d and raised to 400 mg/d after 1 month dramatically improved LCH cerebral infiltration,[6] and, for the multisystemic RDD patient,[7] the manifestations almost completely resolved under 600 mg/d within 6 weeks. Rationale for the use of IM was the

Table 1. Patient characteristics

Case	Sex	Age at diagnosis, y	Age at IM initiation, y	IM duration, mo	IM maximum dose	Previous treatment	IM indication	ECD involvement	Outcome of IM	IM failure
1	M	36	40	12	200 mg/d	Steroids, Vinblastine, MTX, ASCT	Failure of other therapies	Diabetes insipidus; panhypopituitarism; xanthelasma; "coated aorta"; pericardium, left coronary artery; left hydronephrosis; retroorbital masses; lung fibrosis	Stability of all ECD involvement sites; did not tolerate higher doses; treatment stopped by patient	Stable
2	F	63	63	15	600 mg/d	None	CNS and cardiovascular involvements; psychiatric contraindication to IFNα	Diabetes insipidus; severe ataxia (cerebellar mass); hypophysitis; exophthalmos; "coated aorta"	Absence of efficacy after 3 mo of treatment at 200 mg/d justifying adjunction of IFNα (3 M $\times$ 3) due to severity of the disease; brain MRI stable; IFNα not well tolerated (fever, psychiatric disorders) and stopped after 10 mo; worsening of cerebellar involvement, leading to treatment discontinuation.	Worsening
3	F	62	63	7	800 mg/d	None	CNS and cardiovascular involvements	Severe CNS with several focal lesions ("pseudo-meningioma"), ataxia; "pseudo-atrial" tumor; xanthelasma; lung fibrosis; bone pain	Absence of occurrence of new brain focal lesion (the patient had undergone four operations on the brain in the 5 y before treatment initiation), initially better, but worsening of ataxia and bone pain during last 2 mo of treatment; TEP-FDG: new cerebral fixation uptake appeared under treatment, while brain MRI and echocardiography results were stable	Initial stabilization of the disease, before worsening
4	M	60	62	24	200 mg/d	Steroids	Cardiovascular involvement	Bone pain; "coated aorta," celiac trunk, superior mesenteric artery, left subclavian artery, coronaropathy	Persistence of bone pain; history of myocardial infarction in May 2006 (coronary stent); did not tolerate higher doses (visual disturbance).	Worsening
5	M	41	46	6	300 mg/d	Steroids, IFNα, MMF, MTX, ASCT	Failure of other therapies; CNS and cardiovascular involvements	Bone pain; periaortic fibrosis, renovascular HT; severe CNS, ataxia; Hypophysitis	Worsening of ataxia, brain MRI stable; Septic osteomyelitis of the right jaw leading to treatment discontinuation	Worsening
6	M	18	31	15	400 mg/d	2CDA, tandem ASCT	Recurrence 6 y after other therapies	Massive exophthalmos; Voluminous facial mass involving both orbits and the facial sinuses after a 6 y remission after ASCT	Absence of worsening of exophthalmos, which reappeared 6 y after ASCT and remains mild to moderate	Stable

expression of PDGF receptor beta (PDGFr-β) on histiocytes and the inhibition of PDGF kinases by IM.[8-10]

PDGFr-β (Santa Cruz Biotechnology, Santa Cruz, CA) expression was studied on tissue samples from various origins of 37 ECD patients, 11 LCH patients, and 4 RDD by immunostaining on formalin-fixed, deparaffinized 4-μm tissue sections, using commercial kits, LSAB, or the EnVision+DAB system, and an automated immunostainer, according to the manufacturer's instructions (Dako North America, Carpinteria, CA). In 32 of 37 samples (86.5%)—the largest monocentric pathologic analysis of ECD—a positive PDGFr-β expression on histiocytes was observed. Three of the 11 LCH biopsies (27.3%) had histiocytes positive for PDGFr-β. None of the 4 specimens from RDD patients was positive for PDGFr-β.

Six of the 32 ECD patients positive for PDGFr-β, whose disease was severe, potentially life-threatening, multisystemic, and/or refractory to conventional therapy (including IFNα and/or autologous stem cell transplantation) were treated with IM (see Table 1). All 6 patients, followed at the Internal Medicine Department of Pitié-Salpêtrière Hospital, provided written informed consent in accordance with the Declaration of Helsinki. The medical decision to propose a treatment by IM was taken after a collegial discussion, justified by the severity of the disease in all cases and by the resistance to other treatments in 3 cases. The initial dose was 100 mg/d, increasing progressively according to tolerance and treatment efficacy. In one patient, the maximum dose reached was 800 mg/d. Five of the 6 patients received IM only. Median follow-up after IM initiation was 12.5 months (range: 6-24 months) and the maximal median daily dose was 350 mg/d. On the basis of the clinical and the radiologic outcomes, physicians (J.H. and Z.A.) judged the disease was globally "stable" in 2 and "worsening" in 4 cases. Studying the evolution of the "site by site" ECD manifestation under IM we found different response rate according to the sites of involvement. While CNS manifestations often worsened (75%), cardiovascular involvement remained stable in most of the cases (80%). IM was safe, with no major side effects observed.

The sample size of our study is large enough to draw firm conclusions on the almost unvariable presence of PDGFr-β on histiocytes of ECD. Our data, and those previously reported, suggest that the PDGFr-β expression is much more variable in LCH and RDD. Even though IM does not seem to be efficacious in ECD, we cannot rule out a partial efficacy on cardiovascular involvement. It is possible that several patients were too severe to show improvement at the time of treatment initiation, especially those with long-term lasting CNS involvement (case nos. 2, 3, and 5). In some cases doses of IM might not have been high enough (case nos. 1, 4, and 5) compared with higher doses that were given in RDD (400 to 600 mg/d).[7] Tyrosine kinase inhibitors more specific of the PDGFr-β could therefore be promising drugs for the treatment of patients with severe forms of ECD resistant to IFNα therapy.

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