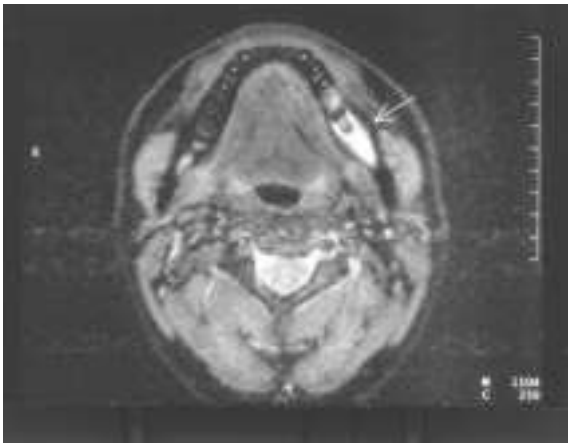

Figure 1. Patient #2. Axial STRI image of the body of the mandible shows a hyperintense lesion on the left side (arrow) and a small focus on the right side.

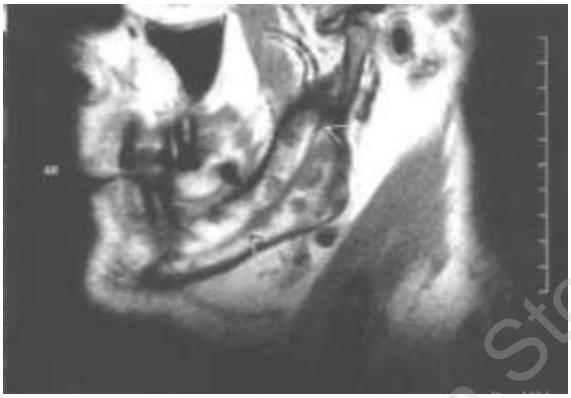

Figure 2. Patient #4. Oblique sagittal T1-weighted image along the ramus of mandible demonstrates multiple round hypointense lesions, as well as their relationship with the mandibular canal (arrowheads). The patient's symptoms could be explained by involvement of the inferior alveolar nerve. The low signal intensity in the mandibular condyle also indicates diffuse infiltration of the bone marrow.

multiple myeloma complained, together with constitutional symptoms, of paresthesia of the right side of the chin. The cerebrospinal fluid was normal and the MRI demonstrated infiltration of the jaw, primarily on the right side. Treated with an autologous stem cell transplantation, he died ten months later .

The appearance of unilateral or bilateral paresthesia and hypoesthesia over the mandibular branch of the trigeminal nerve suggests the diagnosis of this numb chin neuropathy. It may be caused by metastatic involvement of the mental nerve or the lower alveolar nerves of the jaw (50%) and in a smaller proportion by involvement of the proximal mandibular root at the base of the skull or by intracranial leptomeningeal spread. MRI or CT scan of the cranium-mandible area usually shows a neoplastic infiltrate. Bone scans reveal skeletal osseous lesions in the vast majority of patients, although in some instances scans of the mandible can be normal. The cerebrospinal fluid should be examined to rule out meningeal neoplastic infiltration. The malignancies more frequently involved in the development of NCS are breast cancer and aggressive lymphoproliferative syndromes (64-66% and 14-20% respectively in two studies). Generally, NCS appears in association with other symptoms in the context of neoplastic progression and dissemination but can also constitute the first expression of neoplastic disease. In all cases, NCS indicates poor prognosis; our four patients all died within ten months of the onset of the NCS.

The appearance of NCS should prompt a search for malignancy and is a sign of poor prognosis in the oncologic patient.

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Collection of Ph-negative progenitor cells from Ph+ CML patients in complete cytogenetic remission after long-term interferon-α therapy

Sir,

A wider use of autografting in Philadelphia positive chronic myeloid leukemia (Ph+ CML) is prevented by the contamination of blood and marrow with Ph+ cells, accounting in part for recurrence of CML.[1-4] Recently, some studies have shown that Ph-neg progenitor cells can be successfully mobilized by using recombinant human granulocyte colony-stimulating factor (rHuG-CSF) alone in patients who achieve a

Table 1. Clinical and hematologic characteristics of Ph+ CML patients at diagnosis and before G-CSF mobilization.

	At diagnosis					IFNα Therapy	Before G-CSF			
Case/UPN	Sex	Age (yrs)	Sokal's risk	Ph+ (%)	BCR/ABL transcript	Months	Ph+ (%)	WBC (×10⁹/L)	PLTs (×10⁹/L)	Hb (g/dL)
1/7796	M	44	0.645	100	b_2a_2	31	0	1.9	138	13.4
2/10751	M	24	0.469	100	b_2a_2	30	0	5.6	85	14.6
3/3704	M	34	0.791	100	b_2a_2	54	0	2.4	90	15.6
4/8765	F	19	0.550	100	b_2a_2	12	0	3.5	130	13.4
5/8693	M	41	0.684	100	b_3a_2	20	0	3.2	125	12.3
6/7677	M	35	0.581	100	b_3a_2	19	0	4.3	197	14.7
7/10909	F	28	0.506	100	b_3a_2	52	0	2.9	87	14.4
8/11586	M	54	0.952	100	b_3a_2	33	0	3.1	90	15.4
9/11620	F	21	0.733	100	b_3a_2	45	0	2.6	118	11.9

Table 2a. Cell yield and molecular (QC-PCR) analysis of pre-apheresis bone marrow cells and leukapheres in the Ph+ CML patients.

UPN	7796					10751				3704				8765	
Sample	BM	PB				BM	PB			BM	PB			BM	PB
N° apheresis		1	2	3	4		1	2	3		1	2	3		1
WBC (x10⁹/L)		22.5	29.2	31.8	20.0		47.1	34.6	11.0		28.0	30.7	12.0		23.0
CD34/µL		9.0	10.0	8.0	8.0		19.0	17.0	5.0		6.8	7.2	10.0		7.1
Collected MNC (x10⁸/Kg)		2.2	3.0	1.7	1.6		6.4	5.3	1.58		2.0	1.9	0.67		3.1
Collected CD34+ (x10⁶/Kg)		0.45	0.46	0.34	0.12		1.3	1.4	0.3		0.26	0.29	0.19		11.7
BCR/ABL transcript (mol/µgRNA)	4	40.0	40.0	< 4	4.0	< 4	2,800	4.0	<4	< 4	400	<4	< 4	29	40

UPN	8693		7677		10909		11586				11620		
Sample	BM	PB	BM	PB	BM	PB	BM	PB			BM	PB	
N° apheresis		1		1		1		1	2	3		1	2
WBC (x10⁹/L)		29.0		31.0		30.0		34.0	45.0	47.0		30.7	28.3
CD34/µL		7.5		7.3		7.7		7.5	7.1	7.4		17.8	31.0
Collected MNC (x10⁸/Kg)		2.0		11.0		8.3		2.3	2.6	1.0		2.6	2.3
Collected CD34+ (x10⁶/Kg)		5.2		8.8		7.3		0.26	0.29	0.19		1.1	1.2
BCR/ABL transcript (mol/µgRNA)	40	40	400	400	480	40	4,000	400	400	400	<4	40	400

BM: pre-apheresis bone marrow cells; PB: peripheral blood cells.

cytogenetic response with interferon-α (IFN-α).[5-7] Major or complete cytogenetic response and short duration (< 12 months) of IFN-α therapy were apparently the main factors which influenced the mobilization and collection of normal (Ph-neg) progenitor cells. We report here on 9 patients with Ph+ CML in chronic phase, who did not have an HLA-identical sibling, in whom a complete and stable cytogenetic response (100% Ph-neg in at least two consecutive controls based on examination of 20 to 50 metaphases) had been obtained with IFN-α. Hemopoietic progenitors were collected from peripheral blood mobilized by rHuG-CSF (filgrastim), after more than one year of treatment with IFN-α (Table 1). The median

duration of IFN-α treatment prior to study entry was 30 months (range 12-54), and the daily dose administered varied from 3 to 9 MIU (Table 1). Interferon-α was discontinued 15 days before. Filgrastim was administered (s.c) at a dose of 15 mg/kg/day for 5 days. Leukaphereses were then started and performed daily, using a Cobe Spectra blood separator, until the target cell yield was obtained (> 1×10^6 $CD34^+$ cells/kg b.w.). Apheresed cells were then cryopreserved. The Ph+ cell contamination both in the patients' bone marrow and in the leukapheresis products was evaluated with a quantitative competitive PCR technique (QC-PCR).[8] The priming treatment with filgrastim was well tolerated. Bone pain (WHO grade I-II) occurred in three cases. Seven out of 9 patients (78%) yielded more than 1×10^6 $CD34^+$ cells/kg in one (4 cases) or 2 to 4 (3 cases) collections (Table 2). In 5 out of the 9 mobilized cases the levels of BCR/ABL transcript in the first apheresis product were 10 to 700 fold higher than the levels of BCR/ABL transcript measured in the pre-apheresis bone marrow samples (Table 2). In 3 of these 5 patients the amount of BCR/ABL transcript decreased significantly in the subsequent aphereses reaching pre-G-CSF mobilization values (Table 2). Using the QC-PCR to assess the Ph^+ minimal residual disease in the leukapheresis products we found that priming treatment with filgrastim could induce an earlier mobilization of Ph^+ cells. This could be due to functional impairment of adhesion molecules necessary to retain progenitors in the bone marrow microenvironment,[9] or alternatively, to the induction of differentiation of CML cells[10] and their partial elimination by earlier aphereses. No significant correlation (r = 0.0069; p = 0.78) was found between the level of BCR/ABL transcript and the number of $CD34^+$ cells collected. No patient has been autografted as yet, because all patients remain in complete or major cytogenetic remission after collection. We therefore cannot provide data concerning the repopulating ability of the collected $CD34^+$ cells. We did, however, show that Ph-neg $CD34^+$ cells could be collected from patients who were treated with IFNα for a long time, were in cytogenetic remission and had a hypocellular marrow.

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Key words

CML, IFNα, G-CSF, autografting

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All-trans retinoic acid potentiates the *in vitro* inhibitory effects of IFN-α in parental and p210-bcr/abl transfected murine myeloid cell lines

Sir,

Recently, a great deal of interest has been focused on the use of ATRA in the treatment of Ph+ CML.[1-3] Preclinical observations showed that all-trans retinoic acid (ATRA) synergizes with IFNα to induce suppressive effects on Ph+ CML progenitor cells.[4,5] As