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Correspondence

Clara Camaschella, M.D., Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Azienda Ospedaliera San Luigi, 10043 Orbassano, Italy. Phone: international +39-011-9038610 – Fax: international +39-011-9026636 – E-mail: camaschella@ope.net

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Pilot study of combined therapy with interferon-α, arabinosyl cytosine and all-trans retinoic acid in patients with chronic myeloid leukemia in the chronic phase

Sir,

The beneficial effect of IFNα on survival of Ph+ CML patients is known to be associated with the achievement of cytogenetic remission.[1-3] Low-dose arabinosyl cytosine (LDAC)[4] and all-trans retinoic acid (ATRA)[5-10] can increase the response rate to IFNα. This study was designed to evaluate the feasibility of treatment with IFNα, LDAC and ATRA in patients with Ph+ CML in the chronic phase with special attention focused on dose adjustment and side effects. Our observations suggest that if one gives and maintains IFNα at 9 MU/daily or at the maximum tolerated dose, LDAC and ATRA cannot be given at the dose and schedule that were tested in this study.

Eleven consecutive patients received IFNα at a dose of 9 MU/day s.c. and in addition, monthly courses of LDAC (40 mg/day s.c., for 10 days every month, from day 1 to day 10) and ATRA (80 mg/sqm/day p.o., for 10 days every month, from day 20 to day 30) (Table 1). Treatment adjustment was decided every 30 days with the purpose of maintaining IFNα at the maximum tolerated dose. When WBC was 3-3.9$\times10^9$/L or PLT 75-99$\times10^9$ (grade I toxicity), IFNα and ATRA were continued at full dose while the next course of LDAC was purposely omitted; if WBC was 2-2.9$\times10^9$/L or PLT 50-74$\times10^9$ (grade II toxicity), IFNα was reduced to 3 MU/day for the next 30 days, ATRA was kept at full dose and the next course of LDAC was skipped; in case of WBC < 2×10^9 or PLT < 50×10^9 (grade III toxicity), IFNα, LDAC and ATRA were discontinued for the next 30 days, and if the recovery did not take place within 90 days LDAC was stopped permanently. Treatment adjustment for non hematologic toxicity was based on IFNα, LDAC and ATRA related side-effects which were graded according to the WHO scale. In case of grade II toxicity, the dose was reduced by 50% for the next month, after which the full dose was restored. In case of grade III toxicity, the drug was discontinued for the next month and then, if complete recovery occurred, 50% of the dose was given. In case of grade IV toxicity or refusal the drug was discontinued permanently.

During the first 12 months of therapy we observed that: i) LDAC had to be discontinued in the majority of patients (72%) because of persistent leukopenia and/or thrombocytopenia (grade III); ii) ATRA had to be discontinued in 45% of patients, mainly due to headaches (WHO grade III-IV); iii) IFNα was never discontinued and was maintained at a dose of 9 MU/day in 60% of patients. By the 3rd month, all of the drugs had had to be reduced in 5/11 patients (45%) (Table 2). None of the patients experienced bleeding or infectious episodes, or required blood transfusions (the lowest hemoglobin level was 8.2 g/dL). As for the hematologic effects, the majority of patients (82%) achieved and maintained a complete hematologic response[1] and five (45%) obtained a cytogenetic response (Table 3). Two out of the 4 patients who displayed a major cytogenetic response (Ph-neg > 66%) where those who received the combined therapy for a prolonged period of time.

These observations suggest that this combination could be potentially effective in the treatment of Ph+ CML. If one gives and maintains IFNα at 9 MU/daily or at the maximum tolerated dose, LDAC and ATRA[9] cannot be given at the dose and schedule that were tested in this study. To administer this drug combination for a longer time a reduction of either

Table 1. Clinical and hematologic features of the 11 Ph+ CML patients in chronic phase at diagnosis and before starting the combined therapy with IFNα+LDAC+ATRA.

		Hematologic and clinical parameters at diagnosis									*Hematologic and clinical parameters before combined therapy*				
Case	*pts.*	*Sex/ age*	*WBC (x 10^9/L)*	*MB (%)*	*PLT (x 10^9/L)*	*Hb (g/dL)*	*Spleen (cm)*	*Ph+ (%)*	*Sokal risk*	*Previous therapy*	*Months from diagnosis*	*WBC (x10^9/L)*	*MB (%)*	*PLT (x 10^9/L)*	*Hb (g/dL)*	*Spleen (cm)*
1	NC	M/47	208	6	285	9.9	7	100	1.343	IFNα* 8.0 MU/day	2	15	1	152	9.4	4
2	ZC	M/45	14	1	225	13.4	0	100	0.654	IFNα* 6.7 MU/day	2	10.5	0	127	12.7	0
3	DMA	M/28	146	2	164	13.0	3	100	0.622	IFNα* 5.3 MU/day	2	31	2.5	112	12.1	3
4	ZE	M/55	239	0	822	9.9	0	100	0.864	IFNα* 7.9 MU/day	2	13.4	0	147	12.2	0
5	SR	M/35	72	1	127	12.5	3	100	0.596	IFNα* 7.1 MU/day	2	16.1	1	98	11.2	0
6	SA	F/53	164	2	500	9.9	4	100	0.998	IFNα* 7.9 MU/day	2	108	0.5	202	11.1	2
7	TA	F/47	177	2	272	10.0	2	100	0.768	IFNα* 7.0 MU/day	2	13.4	0	161	8.8	0
8	DL	M/52	33	3	206	14.0	2	100	0.860	//	0	62	1	273	13.6	2
9	FA	M/25	150	1	452	11.7	7	100	0.885	HU 17 g. total dose	0.5	83	3	594	9.3	8
10	PV	M/35	280	6	570	10.9	16	100	1.100	HU 50 g. total dose	1	52.7	3	635	11.0	18
11	CG	F/39	280	3	940	11.8	9	100	1.380	HU 30 g. total dose	0.5	35.5	0	1800	10.4	7

**Median daily dose.*

Table 2. Hematologic and non-hematologic drug-related toxicity in the 11 Ph+ CML patients treated with IFNa + LDAC + ATRA.

		Drug discontinuation			*Dose reduction and drug-related side-effects*				
Months from start	*Cases treated with the combined therapy*	*Drug*	*No. cases*	*Causes (no. of pts)*	*Drug*	*No. cases (%)*	*Median dose administered*	*Hematologic (grade)*	*Non-hematologic (grade - WHO)*
3rd	11/11 (100%)				IFNα	5/11 (45)	56%	Leukopenia, Thrombocytopenia (II) (II)	Pain, Diarrhea, Hepatic (II) (II) (II)
					LDAC	7/11 (64)	33%	Leukopenia, Thrombocytopenia (I-II) (I-II)	
					ATRA	6/11 (54)	58%		Headache, Cutaneous (II-III) (III) Xerostomia, Dry skin (I) (I)
6th	6/11 (54%)				IFNα	5/11 (45)	66%	Leukopenia, Thrombocytopenia (II) (II-III)	Diarrhea, Hepatic (II) (III)
		LDAC	4	Leukopenia (1) Vomiting (1) Refusal (2)	LDAC	3/7 (43)	33%	Leukopenia, Thrombocytopenia (I-II) (I-II)	
		ATRA	5	Headache (3) Refusal (1) Cutaneous (1)	ATRA	1/6 (17)	28%		Headache (II-III)
9th	2/11 (18%)				IFNα	4/11 (36)	33%	Leukopenia, Thrombocytopenia (II) (II-III)	Diarrhea, Hepatic (II) (III)
		LDAC	4	Thrombocytopenia (3) Leukopenia (1)	LDAC	1/3 (33)	33%	Leukopenia, Thrombocytopenia (II) (II)	
					ATRA	3/6 (50)	50%		Headache, Dry Skin (II) (I)
12th	2/11 (18%)				IFNα	5/11 (45)	33%	Leukopenia, Thrombocytopenia (II) (II-III)	Diarrhea (II)
					LDAC	1/3 (33)	33%	Leukopenia (II)	
					ATRA	2/6 (33)	40%		Headache (II)

Table 3. Hematologic and karyotypic response in the 11 Ph+ CML patients treated with IFNα+LDAC+ATRA.

Months from start	Complete hematologic response (CHR)	Karyotypic response	Progression to accelerated blastic phase
3rd	9/11 (81%)	//	//
6th	10/11 (91%)	2/11 (18%) case 2 (50% Ph - neg.) case 7 (82% Ph - neg.)	//
9th	10/11 (91%)	3/11 (27%) case 3 (63% Ph - neg.) case 5 (19% Ph - neg.) case 7 (63% Ph - neg.)	//
12th	9/11 (82%)	5/11 (45%) case 2 (78% Ph - neg.) case 3 (70% Ph - neg.) case 7 (74% Ph - neg.) case 8 (25% Ph - neg.) case 10 (72% Ph - neg)	2/11 (18%) cases 1 and 6

IFNα or LDAC and ATRA is required.

Domenico Russo, Luciana Marin, Antonella Bertone, Mario Tiribelli, Nicoletta Testoni,° Giovanni Martinelli°

Chair and Division of Hematology, Department of Medical and Morphological Research and Department of Bone Marrow Transplantation, Udine University Hospital, Udine; °Institute of Hematology and Medical Oncology "L. and A. Seràgnoli", Bologna University, Bologna, Italy

Key words

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Correspondence

Domenico Russo, M.D., Clinica Ematologica, Policlinico Universitario, piazza S. Maria della Misericordia, Udine, Italy. Phone: international +39-0432-559662/64 – Fax: international +39-0432-559661 – E-mail: domenico.russo@drmm.uniud.it

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Reconstitution of alveolar macrophages from donor marrow in allogeneic BMT: a study of variable number tandem repeat regions by PCR analysis of bronchoalveolar lavage specimens

Sir,

In this study, PCR amplification of VNTR regions was used in order to determine the origin of pulmonary alveolar macrophages (PAM) in five BMT patients. Our results show that this technique is feasible allowing the pattern of reconstitution of this cell population to be determined regardless of whether the donor and recipient were sex-matched or not.

The high incidence and severity of pulmonary complications after allogeneic bone marrow transplantation (BMT) led us to carry out systematic bronchoalveolar lavages (BAL), as a guide to pre-emptive therapy.[1] This allowed us to obtain pulmonary alveolar macrophages (PAM) during the first 100 days after BMT. Tissue macrophages derive from terminal differentiation of blood monocytes originating in the bone marrow. This is supported by the demonstration that within 3 months following BMT, host tissue macrophages, including PAM[2] and hepatic Kupffer cells,[3] are replaced by macrophages of donor origin. However, there is some evidence to support the existence of a local lung stem cell population able to differentiate and maintain the number of PAM.[4] Different conditioning schemes may damage these two PAM precursors differently, which could be reflected in another pattern of PAM repopulation after BMT.[4] The demonstration of the bone marrow origin of PAM has been achieved by Y -body detection,[2] or a