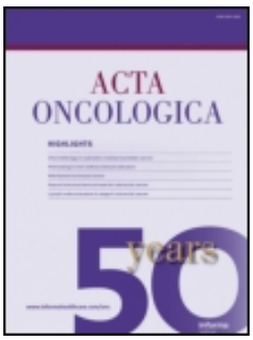

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

Influence of complex variant chromosomal translocations in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors

Fabio Stagno, Paolo Vigneri, Vittorio Del Fabro, Stefania Stella, Alessandra Cupri, Michele Massimino, Carla Consoli, Loredana Tambè, Maria Letizia Consoli, Agostino Antolino & Francesco Di Raimondo

To cite this article: Fabio Stagno, Paolo Vigneri, Vittorio Del Fabro, Stefania Stella, Alessandra Cupri, Michele Massimino, Carla Consoli, Loredana Tambè, Maria Letizia Consoli, Agostino Antolino & Francesco Di Raimondo (2010) Influence of complex variant chromosomal translocations in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors, Acta Oncologica, 49:4, 506-508, DOI: 10.3109/02841861003660031

To link to this article: https://doi.org/10.3109/02841861003660031

Published online: 24 Mar 2010.

Acta Oncologica, 2010; 49: 506–508

informa
healthcare

ORIGINAL ARTICLE

Influence of complex variant chromosomal translocations in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors

FABIO STAGNO[1*], PAOLO VIGNERI[2*], VITTORIO DEL FABRO[1], STEFANIA STELLA[2], ALESSANDRA CUPRI[1], MICHELE MASSIMINO[2], CARLA CONSOLI[1], LOREDANA TAMBÈ[1], MARIA LETIZIA CONSOLI[2], AGOSTINO ANTOLINO[3] & FRANCESCO DI RAIMONDO[1]

Department of Biomedical Sciences, [1]Sections of Hematology and [2]General Pathology, University of Catania, Italy, and [3]Department of Transfusional Medicine, A.O. "Maria Paternò Arezzo", Ragusa, Italy

Abstract

Cytogenetic variants of the Philadelphia (Ph) chromosome can be observed in 5–8% of patients diagnosed with Chronic Myelogenous Leukemia (CML), and usually involve at least one chromosome other than 9 and 22. Despite the genetically heterogeneous nature of these alterations, available data indicate that CML patients displaying complex variant translocations (CVTs) do not exhibit a less favorable outcome as compared to individuals presenting conventional Ph-positive CML. *Patients and methods*. We report our experience with 10 CML patients carrying CVTs among 153 newly diagnosed cases followed at our Institution. *Results and discussion*. Unlike previously published reports, in our series only two CML patients exhibiting CVTs achieved an optimal response to tyrosine kinase inhibitors (TKI) treatment. The remaining eight patients obtained either a suboptimal response or failed drug therapy. Our data suggest that the presence of CVTs at diagnosis might confer an unfavorable clinical outcome, as these genetic alterations might be markers of genomic instability and indicate a higher likelihood of disease progression.

Chronic Myelogenous Leukemia (CML) is a myeloproliferative disease characterized by the presence of the reciprocal translocation t(9;22)(q34;q11), which generates the Philadelphia (Ph) chromosome. The genetic product of this chromosomal alteration is the *BCR-ABL* fusion oncogene that encodes for a cytoplasmic protein with constitutive tyrosine kinase activity. Complex cytogenetic variants of the Ph-chromosome can be observed in 5–8% of newly diagnosed CML patients [1]. These variant translocations usually implicate 9q34,22q11 and at least another breakpoint on a variable chromosome. Despite their genetically intricate nature, available data indicate that complex variant translocations (CVTs) at diagnosis do not represent a negative prognostic factor for CML patients [2]. However such cytogenetic changes could be viewed as the expression of an underlying genomic instability, which is credited for the progression of the disease towards the accelerated and acute phase. It has been previously suggested that the Ph chromosome itself may arise from the unfaithful repair of DNA double strand breaks, and such events may contribute to the occurrence of additional non-random chromosomal abnormalities [3].

The advent of BCR-ABL tyrosine kinases inhibitors (TKIs) such as imatinib (IM) nilotinib (NIL) and dasatinib, has dramatically changed the natural history of CML. Nonetheless, conflicting data have been reported on the clinical relevance of CVTs for TKI therapy. Here we report our experience with 10 CML patients among 153 followed at our institution.

Patients and methods

Between January 2003 and June 2009, 153 patients were diagnosed with CML at our institution and accrued for this study. Clinical, cytogenetic and molecular responses to TKIs were rated according to the European LeukemiaNet (ELN) 2006 guidelines [4]. Among all enrolled patients, we identified 10 cases

*These authors contributed equally to this work.
Correspondence: Fabio Stagno, Department of Biomedical Sciences, Section of Hematology, Ferrarotto Hospital, via S. Citelli 6, 95124-Catania, Italy. Tel: +39 095 7436100. Fax: +39 095 365174. E-mail: fsematol@tiscali.it

(Received 15 October 2009; accepted 28 January 2010)

ISSN 0284-186X print/ISSN 1651-226X online
10.3109/02841861003660031

(6.5% of the total patient population) that displayed CVTs at diagnosis. CML patients with additional chromosomal abnormalities other than CVTs were not included in this series. Bone marrow aspirates, cytogenetic and molecular analyses were performed at conventional time-points [4]. Peripheral blood samples were used for BCR-ABL determination by quantitative real-time polymerase chain reaction according to the suggested recommendations [5] and all BCR-ABL transcripts were measured according to the International standardized Scale (IS). Cytogenetic responses (CyR) were evaluated on no less than 20 marrow cell metaphases after short-term cultures (24-hours) with standard G-banding techniques [6]. Statistical analysis was performed using GraphPad/Instat Software (GraphPad Software Inc, CA, USA) and Fisher's tests and Mann-Whitney tests were employed.

Results and discussion

All patients included in this series were diagnosed as CML in chronic-phase and their main clinical characteristics are listed in Table I. They were nine males and one female, with a median age of 57 years (range 29–74 yrs); five were low Sokal risk and five presented an intermediate Sokal score. Median leukocyte counts (WBC, 1×10^9L) were 100.6 (range 54.4–237), median hemoglobin concentration (Hb, g/L) was 10.9 (range 10.1–15.2) while median platelet counts (PLT, 1×10^9L) were 252 (range 121–825). Median BCR-ABL transcript at diagnosis was 133.156IS. Eight patients received IM standard dose while the other two were enrolled in an investigational trial and received NIL at 800 mg daily. All CVTs involving the Ph chromosome were present at diagnosis. In eight cases three chromosomes were involved (three-way translocation), whilst four chromosomes were implicated in the remaining two patients (four-way translocation). Rearrangements detected involved chromosomes 2, 4, 6, 7, 11, 15, 17, 21, while t (9;22;8) was present in two cases. All patients are still alive and the median follow-up is 25.5 months (range 10–54).

To determine the clinical outcome associated with CVTs in our CML series, we assessed the clinical response after TKI therapy according to ELN recommendations [4] and clustered all subjects in optimal responders and suboptimal responders/drug failures (Table II). Our statistical analysis revealed that patients carrying CVTs at diagnosis exhibited a poor clinical outcome as compared to CML patients without CVTs ($p=0.02$). In fact, among the group displaying CVTs, only two patients (20%) had an optimal response to therapy whereas eight (80%) either achieved a suboptimal response or failed the prescribed TKI. Specifically, seven patients had a cytogenetic (1) or a molecular (6) suboptimal response and one showed primary resistance to IM having failed to obtain a CCyR after 18 months of treatment. On the contrary, in the CVT-negative group, 85 patients (59%) exhibited an optimal response to the assigned TKI. Considering the heterogeneity of the encountered translocations and the limited number of cases, we did not check for further correlations between the type of CVT and the response to TKIs (IM or NIL).

In our patient population, the vast majority (9 of 10) of the complex translocations were observed in male subjects. There were also trends toward the association of CVTs with high WBC counts (100.6 vs. 61.2; $p = 0.05$) low Hb concentrations (10.9 vs. 12.2, $p = 0.8$) and high lactate dehydrogenase levels (947 vs. 870 U/L; $p = 0.5$).

Moreover, since the amount of BCR-ABL transcripts can be representative of the leukemic burden [7], we speculated that high BCR-ABL levels at diagnosis might be indicative of a leukemic clone displaying higher levels of genomic instability [7]. Interestingly, in patients with CVTs the median amount of BCR-ABL at diagnosis was significantly higher (133.1^{IS}) than that of CML patients carrying the conventional 9–22 translocation (66.4^{IS}; $p = 0.03$).

Table I. Baseline clinical and laboratory features of the 10 CML patients carrying CVTs.

PPN	Sex	Age	Sokal score	Euro score	CML phase	BCR-ABL transcript	Karyotype
11	M	29	LOW	LOW	CP	e13a2(b2a2)	46, XY, t (7;9;22)
47	M	44	INT	LOW	CP	e14a2(b3a2)	46, XY, t (2;6;9;22)
51	M	35	LOW	LOW	CP	e14a2(b3a2)	46, XY, t (9;22;15)
69	M	59	INT	HIGH	CP	e13a2(b2a2)	46, XY, t (9;11;21;22)
101	F	64	INT	LOW	CP	e13a2(b2a2)	46, XX,t (9;17;22)
113	M	55	LOW	INT	CP	e14a2(b3a2)	46, XY, t (9;22;8)
124	M	38	LOW	LOW	CP	e13a2(b2a2)	46, XY, t (9;22;8)
136	M	69	INT	INT	CP	e13a2(b2a2)	46, XY, t (4;22;9)
143	M	74	INT	HIGH	CP	e13a2(b2a2)	46, XY, t (9;22;12)
156	M	66	LOW	LOW	CP	e13a2(b2a2)	46, XY, t (9;22;17)

Abbreviation: Chronic Phase (CP).

Table II. Cytogenetic (CyR) and molecular (MolR) responses to tyrosine kinase inhibitors (TKIs).

PPN	TKI	CyR at 6 months (% Ph1)	CyR at 12 months (% Ph1)	CyR at 18 months (% Ph1)	$MolR^{IS}$ at 18 months	Response to TKI
11	IM	0	0	0	0.04	Optimal
47	IM	30	5	NA	NA	Suboptimal CyR at 12 months
51	IM	0	0	0	0.24	Suboptimal MolR
69	NIL	0	0	0	0.25	Suboptimal MolR
101	IM	0	0	0	0.00	Optimal
113	IM	0	0	0	0.28	Suboptimal MolR
124	IM	10	3	1	1.38	Failure
136	NIL	0	0	0	1.20	Suboptimal MolR
143	IM	0	0	0	1.30	Suboptimal MolR
156	IM	25	0	0	0.15	Suboptimal MolR

Abbreviation: Imatinib (IM), Nilotinib (NIL), Not applicable (NA).

In summary, the genesis and the prognostic significance of CVTs in CML remain an unsettled issue [8,9]. The ELN recommendations suggest that additional cytogenetic abnormalities in the Ph-positive clone should be interpreted as warnings, possibly indicative of an evolving disease [4]. Our data are consistent with the hypothesis that complex variant translocations involving the Ph chromosome are associated with a higher degree of genomic instability and a more aggressive form of CML, thus conferring an unfavorable clinical outcome.

Declaration of interest: The authors declare no competing financial interests.

References

[1] Heim S, Billström R, Kristoffersson U, Mandahl N, Strömbeck B, Mitelman F. Variant Ph translocations in chronic myeloid leukemia. Cancer Genet Cytogenet 1985;18: 215–27.

[2] Richebourg S, Eclache V, Perot C, Portnoi MF, Van den Akker J, Terré C, et al. Mechanisms of genesis of variant translocation in chronic myeloid leukemia are not correlated with ABL1 or BCR deletion status or response to imatinib therapy. Cancer Genet Cytogenet 2008;182:95–102.

[3] Penserga ET, Skorski T. Fusion tyrosine kinases: A result and cause of genomic instability. Oncogene 2007;26:11–20.

[4] Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, et al. Evolving concepts in the management of chronic myeloid leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 2006;108:1809–20.

[5] Hughes T, Deininger M, Hochhaus A, Branford S, Radich J, Kaeda J, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: Review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108:28–37.

[6] Mitelman F. ISCN: An international system for human cytogenetic nomenclature. Basel: S. Karger; 1995.

[7] Marin D, Khorashad JS, Foroni L, Milojkovic D, Szydlo R, Reid AG, et al. Does a rise in the BCR-ABL1 transcript level identify chronic phase CML patients responding to imatinib who have a high risk of cytogenetic relapse? Br J Haematol 2009;145:373–5.

[8] Gorusu M, Benn P, Li Z, Fang M. On the genesis and prognosis of variant translocations in chronic myeloid leukemia. Cancer Genet Cytogenet 2007;173:97–106.

[9] El-Zimaity MM, Kantarjian H, Talpaz M, O'Brien S, Giles F, Garcia-Manero G, et al. Results of imatinib mesylate therapy in chronic myelogenous leukaemia with variant Philadelphia chromosome. Br J Haematol 2004; 125:187–95.