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ORIGINAL ARTICLE

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Anagrelide and imatinib mesylate combination therapy in patients with chronic myeloproliferative disorders

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Abstract *Purpose*: The tyrosine kinase inhibitor imatinib mesylate inhibits the function of the Bcr-Abl oncoprotein associated with Philadelphia-positive chronic myelogenous leukemia (CML). Anagrelide suppresses megakaryocyte proliferation and differentiation. The objectives of this study were to investigate the feasibility and safety of imatinib mesylate and anagrelide combination therapy in patients with Ph-positive CML or chronic myeloproliferative disorders (MPD) with persistent thrombocythemia. *Methods*: This study was a retrospective review of all available records of patients with chronic MPD presenting to the M.D. Anderson Cancer Center between October 1998 and May 2002, treated with imatinib mesylate combined with anagrelide. *Results*: Of 22 patients identified, 18 had Ph-positive CML (chronic phase, 16 patients; accelerated phase, 2 patients), 1 had agnogenic myeloid metaplasia (AMM), 2 had essential thrombocythemia (ET) and 1 had MPD transformed into refractory anemia with excess blasts (RAEB). The median age was 57 years (range 26–82 years). The median dose of imatinib mesylate administered was 400 mg (range 300–800 mg) and the median dose of anagrelide was 1.5 mg (range 0.5–4.0 mg). Imatinib mesylate and anagrelide combination therapy was feasible and tolerable. Of the 18 patients with Ph-positive CML, 15 in chronic phase and 1 in accelerated phase achieved a complete hematologic response (CHR), and 9 of the 18 achieved cytogenetic response (complete in 8 patients). No responses were noted in patients with AMM, ET or MPD transformed into RAEB. *Conclusions*: The combination of imatinib mesylate and anagrelide was safe and was associated with an 89% CHR rate in patients with CML in chronic phase and persistent thrombocythemia.

Keywords Anagrelide · Imatinib mesylate · Combination · Myeloproliferative disease

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Introduction

The reciprocal translocation t(9;22)(q34;q11) generates the Philadelphia (Ph) chromosome that fuses two normal genes, *bcr* and *c-abl*, and produces the Bcl-abl hybrid oncogene [1]. Imatinib mesylate (Gleevec, STI571) inhibits the Bcr-Abl tyrosine kinase, which plays a critical role in the pathogenesis of chronic myelogenous leukemia (CML) [2, 3]. In vitro and in vivo studies have demonstrated that imatinib mesylate selectively inhibits the proliferation of cells expressing Bcr-Abl [2, 3]. Recently published studies have demonstrated that imatinib mesylate improves the outcome of patients with Ph-positive CML [3, 4, 5, 6, 7, 8, 9, 10, 11, 12]. In vitro studies also suggest that imatinib mesylate causes variable degrees of growth suppression of myeloid and erythroid progenitors [13], suggesting that imatinib mesylate may have activity in other myeloproliferative disorders (MPDs) [13, 14].

Anagrelide hydrochloride (Agrylin, Shire Pharmaceuticals) is an oral imidazoquinazoline agent with selective thrombocytopenic effect, sparing the other marrow cell lineages [15, 16]. It reduces the megakaryocyte mass and ploidy, reducing the substrate available to form circulating platelets [17]. It also decreases the platelet counts and turnover rate by suppressing both megakaryocyte proliferation and differentiation [17].

Based on these observations, imatinib mesylate and anagrelide therapy may improve the outcome of patients with Ph-positive CML or patients with other MPDs. We thus analyzed the safety and toxicity of imatinib

mesylate and anagrelide combination therapy in patients with Ph-positive CML and chronic MPDs.

Materials and methods

The database of the Department of Leukemia of the University of Texas, M.D. Anderson Cancer Center was searched for patients treated with imatinib mesylate combined with anagrelide. The database of the Department of Pharmacy was also searched for patients with chronic MPDs treated with anagrelide from October 1998 to May 2002 and then condensed to those who had received concomitant imatinib mesylate. Patients treated with concomitant therapy for less than a month were excluded from the analysis. All records were reviewed for clinical presentation, laboratory tests, treatment and outcome. Patient evaluation included history, physical examination, complete blood count, platelet counts, and differential, biochemical profile, bone marrow aspirates and biopsies, cytogenetic analysis of bone marrow and available reports of chest radiography and computerized tomography of head and neck, chest, abdomen and pelvis.

A signed informed consent was obtained form all patients who were treated on protocols investigating imatinib mesylate either as a BCR-ABL inhibitor or a c-Kit/PDGFR inhibitor in other MPD, in keeping with the policies of the M.D. Anderson Cancer Center.

Therapy

Imatinib mesylate was administered orally at doses ranging from 300 to 800 mg daily, with doses adjusted according to published guidelines, as previously described [4, 18, 19, 20]. In patients with persistent thrombocythemia (platelet counts $\geq 600\times10^9$/l for more than 1 month) anagrelide was added at a daily dose of 0.5–4.0 mg. Treatment was continued until the disease was considered unresponsive, death, a change to more definitive therapy (e.g., second stem cell transplantation), or the appearance of unacceptable toxic effects that did not respond to dose modifications.

Endpoints

Complete hematologic response (CHR) was defined as the normalization of peripheral blood cell counts and differential counts and the disappearance of all signs and symptoms of CML for at least 4 weeks. Cytogenetic responses were categorized as complete (no Ph-positive metaphase cells in bone marrow or blood samples), partial (1–34% Ph-positive cells), or minor (35–90% Ph-positive cells). For patients with agnogenic myeloid metaplasia (AMM) and essential thrombocythemia (ET), CHR was defined as normalization of the peripheral blood cell counts and absence of signs or symptoms of the disease, for at least 4 weeks. Survival was measured from the time of initiation of imatinib mesylate and anagrelide combination therapy to death from any cause, or last follow-up. Failure-free survival (FFS) was defined as the time from time of diagnosis until progression, relapse, or last contact. Deaths without evidence of progression were censored in the FFS analysis. Survival curves were estimated using the Kaplan-Meier method [21]. Adverse events were graded in accordance with the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 (http://ctep.info.nih.gov).

Results

The database searches identified 22 patients treated with imatinib mesylate and anagrelide. The pretreatment characteristics of the 22 patients are summarized in Table 1. The median age was 57 years (range 26–82 years). Five patients (23%) were older than 60 years. In 18 patients anagrelide was added after a median of 0.4 months (range 0–36 months) following initiation of imatinib mesylate therapy. Four patients (CML in accelerated phase, one patient; CML in second chronic phase, one patient; CML in early chronic phase, one patient; and ET, one patient) were on anagrelide therapy at the time of initiation of imatinib mesylate. Of the 22 patients, 18 had Ph-positive CML (early chronic phase, five patients; late chronic phase, ten patients; second chronic phase, one patient; accelerated phase, two patients), one patient had AMM, two patients had ET and one patient had MPD transformed into refractory anemia with excess blasts (RAEB). The median dose of imatinib mesylate administered was 400 mg (range 300–800 mg) and the median dose of anagrelide was 1.5 mg (range 0.5–4.0 mg).

Table 1 Pretreatment characteristics of patients treated with imatinib mesylate and anagrelide ($n = 22$)

	Median (range)	No. (%) of patients
Age (years)	57 (26–82)	
WBC ($\times10^9$/l)	13.6 (3.4–74.6)	
Hemoglobin (g/dl)	11.7 (7.9–13.5)	
Platelets ($\times10^9$/l)	1027 (629–1997)	
Bone marrow blasts (%)	4 (0–15)	
Bone marrow cellularity (%)	92.5 (50–100)	
LDH (IU/L)	743 (385–2981)	
Creatinine (mg/dl)	1 (0.6–1.8)	
Bilirubin (mg/dl)	0.4 (0.2–1.1)	
SGPT (IU/l)	15 (12–94)	
Albumin (g/dl)	3.9 (3.1–4.3)	
Diagnosis		
Ph^+-CML—early chronic phase		5 (22)
Ph^+-CML—late chronic phase		10 (45)
Ph^+-CML—second chronic phase		1 (5)
Ph^+-CML—accelerated phase		2 (9)
AMM		1 (5)
ET		2 (9)
MPD-RAEB		1 (5)
Male/female		8/14 (36/64)
Cytogenetics		
t(9;22)		16 (73)
t(9;22) and additional chromosome abnormalities		2 (9)
del(13)		1 (5)
Normal		3 (13)
Prior therapy		
Hydroxyurea		11 (50)
Interferon		9 (41)
Pegylated interferon		3 (14)
Interferon + Ara-C		8 (36)
Interferon + pegylated Ara-C		2 (9)
Farnesyl transferase inhibitors (R115777)		2 (9)
Homoharringtonine		1 (5)
Ara-C + 6-thioguanine		1 (5)
Troxacitabine		1 (5)

Response

Of the 18 patients, 16 (89%) with Ph-positive CML achieved CHR. The median time to CHR was 0.8 months (range 0.4–4.3 months). Response by diagnosis is shown in Table 2. No responses were noted in patients with AMM, ET or MPD transformed into RAEB. Of the 18 patients, 8 (44%) with CML achieved complete cytogenetic response and 1 (6%) had a partial cytogenetic response. The characteristics of patients who responded are shown in Table 3. All responders were Ph-positive. No difference in the dosage of imatinib mesylate and anagrelide was noted between the responders and non-responders.

Survival and failure-free survival

At the time of this report, the median follow-up of surviving patients was 17 months (range 2–35 months). Two patients had died. One patient with CML in second chronic phase died from sepsis and one patient with CML in late chronic phase died from cerebral bleeding. The median survival had not been reached. The 2-year overall survival was 88%. When the analysis was limited to patients with CML only, the 2-year survival was 86% (Fig. 1).

Treatment failure occurred in 5 of the 16 patients who achieved CHR; most of these patients received salvage therapy with other regimens. The median time to failure was 31 months and the 2-year FFS was 71% (Fig. 2).

Toxicity

Imatinib mesylate and anagrelide caused grade 3/4 toxicity as follows: thrombocytopenia in three patients (14%), neutropenia in two patients (9%), anemia in one patient (5%), rash in one patient (5%), weight gain in one patient (5%), peripheral edema in one patient (5%), and hyperuricemia in one patient (5%). There was one toxic death from sepsis and multiorgan failure. Grade 1/2 non-hematologic toxicity included peripheral edema in seven patients (32%), fatigue in seven patients (32%), periorbital edema in five patients (23%), skin rash in five patients (23%), arthralgias in five patients (23%), headache in three patients (14%), nausea/vomiting in two patients (9%), muscle cramps in two patients (9%), weight gain in two patients (9%), and diarrhea in one patient (5%).

Discussion and conclusion

This retrospective study suggests that combination therapy of imatinib mesylate and anagrelide is feasible and tolerable. Imatinib mesylate and anagrelide combination therapy was associated with an 89% CHR rate in patients with Ph-positive CML, but had no activity in the four patients with Ph-negative MPDs (ET, AMM or MPD-RAEB).

Single-agent imatinib mesylate has dramatically improved the prognosis of patients with Ph-positive CML [4, 6, 19, 22]. It induces higher rates of hematologic and cytogenetic response in patients with CML in chronic phase than interferon, or homoharringtonine, either alone or in combination with low-dose cytarabine [4]. While the molecular remission rates achieved with imatinib mesylate are being evaluated in ongoing studies, preliminary data suggest that after achieving complete cytogenetic remission and while continuing on therapy, higher rates of molecular remission are achieved in patients with CML in chronic phase treated with imatinib mesylate compared to those treated with interferon plus cytarabine, as first-line therapy [5]. The CHR and cytogenetic response rates are consistent with previously published data on imatinib mesylate monotherapy [4].

Imatinib mesylate has shown very little activity in patients with Ph-negative MPDs [13]. In the current study, none of the four patients with ET, AMM, or MPD-RAEB responded to treatment. This finding is consistent with the results of another study in which imatinib mesylate did not induce responses in patients with myelofibrosis with myeloid metaplasia [13]. In contrast, durable responses have been reported in patients with MPD carrying the fusion gene linking TEL (now known as ETV6) with platelet-derived growth factor receptor beta (PDGFRB) [14].

Anagrelide is increasingly used, and has been approved, as a treatment for patients with ET younger than 60 years of age [16], and is associated with response rates of over 90% in these patients [15, 23, 24]. These responses are durable with a median maintenance dose of approximately 2–2.5 mg daily [25]. In the current study, imatinib mesylate was combined with anagrelide with the

Table 2 Response to imatinib mesylate and anagrelide according to diagnosis

Diagnosis	*n*	CHR (%)	Complete cytogenetic response (%)	Partial cytogenetic response (%)
Ph^+-CML—early chronic phase	5	5 (100)	4 (80)	1 (20)
Ph^+-CML—late chronic phase	10	9 (90)	4 (40)	0
Ph^+-CML—second chronic phase	1	1 (100)	0 (0)	0
Ph^+-CML—accelerated phase	2	1 (50)	0 (0)	0
AMM	1	0 (0)	N/A	N/A
ET	2	0 (0)	N/A	N/A
MPD-RAEB	1	0 (0)	N/A	N/A

Table 3 Characteristics of patients who responded to imatinib mesylate and anagrelide therapy (at the time of this report)

Age (years)	Sex	Diagnosis	Time from diagnosis (years)	Cytogenetics	Anagrelide (mg/day)	Imatinib (mg/day)	Cytogenetic response	Failure status	Time to failure (months)	Survival status	Survival (months)
45	F	CML—late chronic	0.8	t(9;22)	1.5	800	Complete	Non-failure	12.0	Alive	13.3
69	F	CML—late chronic	2.8	t(9;22)	0.5	400	Complete	Non-failure	17.7	Alive	18.7
82	F	CML—second chronic	1.9	t(9;22)	1.0	600	None	Non-failure	7.6	Dead	9.9
26	M	CML—accelerated	3.3	t(9;22)	1.5	600	None	Failure	6.7	Alive	35.1
42	F	CML—late chronic	6.7	t(9;22)	1.5	300	None	Non-failure	10.8	Alive	11.9
58	M	CML—early chronic	0.7	t(9;22)	2.0	400	Complete	Non-failure	26.1	Alive	26.8
60	F	CML—late chronic	3.4	t(9;22), +19	1.0	600	None	Failure	18.6	Alive	20.4
73	F	CML—late chronic	10.1	t(9;22)	1.0	400	Complete	Non-failure	22.1	Alive	22.7
57	F	CML—late chronic	2.2	t(9;22)	2.0	400	Complete	Non-failure	5.3	Alive	5.8
44	M	CML—early chronic	1.2	t(9;22)	1.0	400	Partial	Failure	13.5	Alive	16.6
49	M	CML—early chronic	0.8	t(9;22)	2.0	400	Complete	Non-failure	33.6	Alive	34.4
76	M	CML—late chronic	4.9	t(9;22)	2.0	400	None	Failure	30.9	Alive	34.7
58	F	CML—late chronic	3.3	t(9;22)	1.5	400	None	Non-failure	14.7	Dead	15.3
61	F	CML—late chronic	5.9	t(9;22)	1.0	300	None	Failure	25.3	Alive	27.5
40	F	CML—early chronic	0.2	t(9;22)	3.0	300	Complete	Non-failure	16.1	Alive	17.4
34	M	CML—early chronic	0.1	t(9;22)	1.5	400	Complete	Non-failure	15.4	Alive	15.8

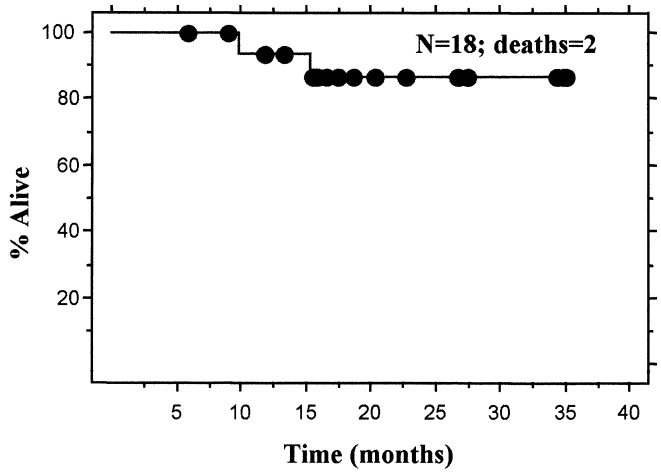

Fig. 1 Overall survival in 18 patients with Ph-positive CML treated with imatinib mesylate and anagrelide

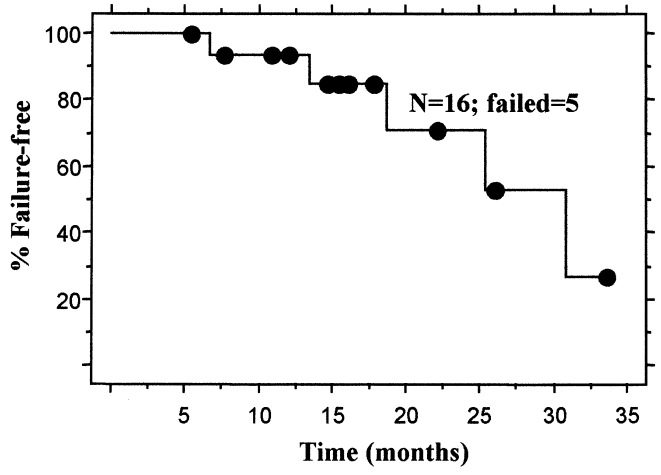

Fig. 2 Failure-free survival in 16 patients who responded to imatinib mesylate and anagrelide therapy

expectation that thrombocythemia might be more smoothly and rapidly controlled. Although this study had certain limitations, e.g. retrospective review, small numbers of patients, and absence of a control group, it suggests that the combined therapy is safe and may be associated with a short time to response (median 0.8 months, range 0.4–4.3 months). In a previous study in patients with CML in accelerated phase, 1 month of imatinib mesylate therapy was required before hematologic responses were seen [26]. It is however possible that some bcr-abl-positive patients with thrombocytosis would have responded to imatinib mesylate with more protracted therapy. Larger studies are needed to define those patients who merit combination therapy with anagrelide.

The most common toxicities observed in the current study are consistent with previously published data on imatinib mesylate monotherapy [4, 6, 19]. Myelosuppression is dose-related and common non-hematologic toxicities are nausea, vomiting, diarrhea, edema, muscle cramps, rash and headache [4]. Fluid retention may be severe, causing pleural effusions, pericardial effusions, pulmonary edema, ascites, rapid weight gain or significant peripheral edema [27]. In addition, anagrelide causes vasodilation-related and positive inotropic effects to the central nervous system, and cardiovascular and gastrointestinal systems, such as headache, fluid retention, hypotension, tachycardia, arrhythmias, diarrhea, nausea and abdominal pain [16].

It is somewhat surprising that in those patients on study who were bcr-abl-negative, i.e. being treated with imatinib mesylate as a potential c-kit or PDGFR inhibitor, the elevated platelet count seemed relatively refractory to anagrelide. While there are isolated reports of bcr-abl-negative patients with MPD showing response to imatinib mesylate, the great majority of these patients do not respond to this therapy.

In conclusion, this study suggests that imatinib mesylate and anagrelide combination therapy is feasible and tolerable, and can control the thrombocytosis in some patients with bcr-abl chronic-phase CML. Further investigation of imatinib mesylate and anagrelide combination therapy is warranted.

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