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Chronic myeloid leukemia patients who develop grade I/II pleural effusion under second-line dasatinib have better responses and outcomes than patients without pleural effusion

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ABSTRACT

Dasatinib is a potent second generation TKI, and it is widely used in patients with CML, both in the up-front setting and failure after imatinib. Lymphocytosis in cases receiving dasatinib therapy has been shown to be associated with pleural effusion (PE) and better outcome. Although patients who gather lymphocytosis during dasatinib have superior responses, there is only little data about the correlation between PE, response rates, and survival. In order to answer this question, the aim of our study was to determine the frequency of PE and lymphocytosis among our CML patients receiving second-line dasatinib, and to compare the responses and outcomes between patients with or without PE. There were 18 patients (44%) who developed PE, in a total of 41 patients, with a median time of 15 months. Lymphocytosis was observed in nine patients (9/41, 22%) with a median duration of 6.5 months of dasatinib treatment. There were fourteen patients with at least one comorbidity that may play a role in the generation of PE. The cumulative MMR and CCyR rates were greater in PE+ patients ($p < 0.05$). The PFS was significantly higher in PE+ group than PE− patients ($p = 0.013$), also the OS was higher among PE+ patients than PE− group ($p = 0.042$). In patients with a grade I/II PE, and durable responses under dasatinib, performing the management strategies for the recovery of effusion, together with continuing dasatinib can be a reasonable choice mainly in countries where third generation TKIs are not available. But alternative treatment strategies such as nilotinib or third generation TKIs can be chosen in patients with grade III/IV PE especially if the quality of life is severely affected.

1. Introduction

Dasatinib (Sprycel; Bristol-Myers Squibb, New York, USA) is a novel, orally available second generation tyrosine kinase inhibitor (TKI) which is approved for the treatment of *BCR-ABL1* positive chronic myeloid leukemia (CML) in chronic (CP), and accelerated (AP) phases, and blast crisis (BC) in the up-front setting as well as after imatinib failure, and also for the treatment of Philadelphia (Ph) chromosome positive acute lymphoblastic leukemia (ALL) after imatinib failure [1]. Dasatinib is an inhibitor of multiple tyrosine kinases, including the oncogene fusion protein *BCR-ABL1*, and also inhibits Src family of kinases (SFKs) and platelet-derived growth factor receptor, beta polypeptide (PDGFR-b) [2]. Imatinib (Gleevec; Novartis, East Hanover, New Jersey, USA) induces complete cytogenetic responses (CCyR) in approximately 80% of patients with CP-CML [3,4]. Although the responded patients usually maintain their responses, some patients may eventually develop resistance [5].

Dasatinib is 325 times more potent in vitro against unmutated *BCR-ABL1* than imatinib [2], and dasatinib is able to bind to both the active and inactive conformations of the ABL kinase domain, which is why it is effective against many imatinib-resistant cases. Although dasatinib is a potent and efficacious drug, patients are also subject to various adverse events (AEs). The most common

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AEs are gastrointestinal, peripheral edema, and myelosuppression [6]. Lymphocytosis can be seen during dasatinib treatment [7,8], and this phenomenon is thought to be associated with superior response rates [9,10]. Fluid retention has been associated with imatinib, dasatinib, and nilotinib, but pleural effusions (PEs) may be more common with dasatinib [11]. The real-life data with CML patients receiving dasatinib after imatinib failure is associated with higher incidence of pleural and pericardial effusions [12,13], than reported in clinical trails. The therapeutic activity of dasatinib against the Src kinases is thought to be responsible for several of its "off-target effects". Also it has been shown that lymphocytosis can accompany PE [8,10], and these two manifestations are shown to be in a strong association. Although patients who gather lymphocytosis during dasatinib treatment have superior responses, there is only little data about the correlation between PE, response rates, and survival [11]. In order to answer this question, the aim of our study was to determine the frequency of PE and lymphocytosis among our CML patients receiving second-line dasatinib, and to divide these patients into two groups (i.e. patients with or without PE), and compare these groups by means of responses and outcomes. Also we wanted to determine the effusion management strategies in our patient cohort.

2. Patients and methods

2.1. Study population

Forty-one CML patients who were in CP at diagnosis, and received dasatinib due to resistance or intolerance to imatinib were enrolled in the study. Patients' demographics, disease risk scores, comorbidities [including preexisting cardiac disease, renal insufficiency, hypertension and chronic obstructive pulmonary disease (COPD)], dasatinib dose, dosing intervals and treatment durations, durations of imatinib therapy prior to dasatinib, and if any, treatments prior to imatinib (including interferon (IFN), cytarabine (Ara-C), and hydroxyurea (HU), but excluding short term HU use for cytoreduction) and follow-up periods were noted from the patients' files retrospectively (Table 1). The efficacy of the treatment was evaluated using standard hematologic, molecular and bone marrow cytogenetic assessments to determine rates of complete hematologic response (CHR), major cytogenetic response (MCyR), CCyR, and major molecular response (MMR).

2.2. Responses to TKIs and CML phases

Imatinib response was evaluated according to the criteria recommended by the European LeukemiaNet (ELN) [14]. Molecular response (MR) was classified based on *BCR-ABL1* to control gene transcript ratios, expressed on the International Scale, and these tests were performed in Istanbul University, Institute for Experimental Medicine, Department of Genetics. MMR was defined as ratios $\leq$0.1%. Cytogenetic response based on bone marrow assessment was classified as complete (CCyR; 0% Ph+ cells), partial (PCyR; >0 to 35% Ph+ cells), minor (>35 to 65% Ph+ cells), minimal (>65 to 95% Ph+ cells), and none (>95 to 100% Ph+ cells). A MCyR was defined as achieving either a CCyR or a PCyR. The cumulative incidence of MMR during the follow-up periods was calculated. CML phases were defined as described elsewhere [14,15]. Patients with BC, had either received dasatinib alone or in combination with an induction chemotherapy.

2.3. Definitions of pleural effusion and lymphocytosis

Chest X-ray was performed before initiating dasatinib, and then when necessary during the follow-up, for example in patients with relevant pulmonary symptoms, such as chest pain, dyspnea, and dry cough or when findings of PE on physical examination were present. PE was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs Version 3.0 as follows: grade I, asymptomatic; grade II, symptomatic, with any intervention such as diuretics or up to two therapeutic thoracenteses indicated; grade III, symptomatic and supplemental oxygen, more than two therapeutic thoracenteses, tube drainage, or pleurodesis indicated; and grade IV, life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated) [16].

In order to determine the lymphocytosis frequency in our patient cohort, we evaluated the complete blood counts and absolute blood lymphocyte count of each patient for each visit, and lymphocytosis was defined as an absolute lymphocyte count greater than 3.6×10^9/L on at least two occasions after more than 4 weeks of dasatinib therapy [10]. For this analysis, elevated lymphocyte counts within the first 4 weeks of dasatinib therapy were not included in the determination of lymphocytosis. Mean lymphocyte counts in groups of patients were calculated from mean values for all absolute lymphocyte counts determined after the first 4 weeks of dasatinib therapy in each patient.

2.4. Statistical analysis

We calculated the duration of overall survival (OS) from the date of diagnosis until the time of death or last follow-up. The duration of progression-free survival (PFS) was calculated from the onset of dasatinib until the date of progression (i.e. loss of molecular and/or cytogenetic responses, reaching to advanced disease phases or switching to any other treatment). The Student's *t* test was used for the comparison of the qualitative values. The response rates between two groups were compared by using chi-square test. We used the Kaplan–Meier method [17] to determine the probability of OS or PFS and compared by using the log-rank test. All tests were two-sided, and $p < 0.05$ was considered as statistically significant. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows v.13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Twenty-one patients were female (51%), and the median age of the patient cohort was 52 years (range, 18–84 years). There were eighteen patients (44%) who developed PE (PE+), and PE− group consisted of 23 patients with no PE under dasatinib. The median ages of PE+ and PE− groups were 55.5 and 51 years, respectively ($p > 0.05$) (Table 1). In PE− group, advanced disease (AP + BC) was more frequent than in PE+ patients (8 vs. 2, $p = 0.01$). The mean follow-up for PE+ and PE− groups were 92.3 and 99.2 months, respectively ($p > 0.05$).

The percentages for any other treatment prior to imatinib were 28% in PE+ patients, and 48% among PE− cases ($p > 0.05$). The starting dose of imatinib was 400 mg/day in all patients, and in both groups, the median time of imatinib treatment was similar (31.5 vs. 30.5 months) ($p > 0.05$). The reason for switching from imatinib to dasatinib was resistance (both primary and secondary) in 38 patients, and intolerance in three. In both patient groups, the starting doses of dasatinib were 100 mg and 140 mg daily according to the disease phases (i.e. 100 mg/day in CP, and 140 mg/day in AP and BC), and dose adjustments were required for hematological and/or pulmonary toxicities. Although the daily mean dosage of dasatinib was higher in PE− than PE+ patients (90 mg vs. 79.25 mg), this difference did not reach statistical significance ($p = 0.06$). Patients in PE+ group had received dasatinib for a longer median duration of time when compared to PE− group (35.5 months vs. 14 months) ($p < 0.05$).

3.1. Pleural effusions and lymphocytosis

The median time to PE generation was 15 months (range, 2–35 months), and among the patients with a PE, 4 patients (22%) had grade I, twelve (67%) had grade II and two (11%) with grade III effusions. There were no patients with a grade IV PE. In four patients (22%), there was pericardial effusion accompanying PE.

Lymphocytosis was observed in nine patients (9/41, 22%) with a median duration of 6.5 months of dasatinib treatment (range, 2–12 months). Seven of these patients were in PE+ group, whereas the other two cases did not develop an effusion ($p < 0.05$) (Table 1).

3.2. Comorbidities and pleural effusion generation

In the patient cohort, there were fourteen patients (14/41, 34%) with at least one comorbidity that may play a role in the generation of PE, with five patients having more than one. The frequencies of comorbidities among PE+ and PE− groups were 39% and 30%, respectively, and the comorbidities were more frequently observed in patients with PE ($p < 0.05$) (Table 1).

Table 1
The demographics and clinical features of the patients. (PE, pleural effusion; M, male; F, female; CML, chronic myeloid leukemia; CP, chronic phase; AP, accelerated phase; BC, blastic crisis; MMR, major molecular response; CCyR, complete cytogenetic response.).

Parameter	PE (+) (n = 18)	PE (−) (n = 23)	p value
Age, years median (range)	55.5 (33–84)	51 (18–81)	>0.05
Gender, M/F	9/9	11/12	>0.05
CML phase at the start of dasatinib, CP/AP/BC	16/0/2	15/4/4	0.01
Sokal score, low/intermediate/high	5/6/7	7/8/8	>0.05
Any treatment prior to imatinib, yes/no	5/13	12/11	>0.05
Follow-up duration, month mean (range)	92.3 (24–204)	99.2 (15–177)	>0.05
Duration of imatinib treatment, month median (range)	31.5 (2–89)	30.5 (4–80)	>0.05
Duration of dasatinib treatment, monthmedian (range)	35.5 (5–64)	14 (1–55)	<0.05
Dasatinib dose, mg/day mean (range)	79.25 (50–140)	90 (20–140)	0.06
Comorbidities,[a] ratio (%)	7/18 (39)[b]	7/23 (30)[c]	<0.05
Lymphocytosis, >3.6 × 10^9/L ratio (%)	7/18 (39)	2/23 (9)	<0.05
MMR, ratio (%)	12/18 (67)	5/18 (28)	<0.05
CCyR, ratio (%)	14/18 (78)	6/18 (33)	<0.05

The starting doses of dasatinib were 100 mg and 140 mg daily according to the disease phases, and dose adjustments were required for pulmonary and/or hematological toxicities. These doses are the mean dose for the entire follow-up period.
[a] Cardiac disease, renal insufficiency, hypertension and chronic obstructive pulmonary disease.
[b] Three patients had >1 comorbidities.
[c] Two patients had > 1 comorbidities.

3.3. Management of pleural effusions

In patients with grade III PE, dasatinib was interrupted, and furosemide and glucocorticosteroids were administered. Therapeutic thoracenteses and tube drainage were required in both of them as well. Dasatinib was restarted with a lower dose (70 mg/daily) in one of them (patient #5), during the follow-up PE did not reoccur and the patient maintained MMR and CCyR (Table 2). The other patient was switched to nilotinib due to the persistence of PE.

There were 16 patients with grade I/II PE, of which no other intervention was performed in 4 (patients #3, #11, #12, and #15) other than interrupting dasatinib treatment, and the PEs improved. After restarting dasatinib, one of those patients (patient #2) redeveloped PE, which was then managed with furosemide and glucocorticosteroids, dasatinib was discontinued and the patient then fully recovered.

In the remaining 12 patients, dasatinib therapy was interrupted and furosemide plus glucocorticosteroids were initiated, and effusions were totally resolved in all of them. After the resolution of PE, dasatinib was restarted in all of them with a lower dose (i.e. 50 mg or 70 mg daily) and then escalated to the actual dosage. In four of those patients (patients #7, #10, #16, and #17) PE reoccurred, so they were switched to nilotinib, whereas seven of them did not develop PE during the follow-up. Although dasatinib was interrupted with the administration of furosemide and glucocorticosteroids, PE persisted in patient #14, and this patient had received HU because nilotinib was not given due to the prolongation of QTc and he had no suitable donor for allograft. In patient #13, the PE was regressed with the cessation of dasatinib together with furosemide and glucocorticosteroid administration. He had a suboptimal response under dasatinib, and because he experienced a severe AE with nilotinib, INF/Ara-C was initiated thereafter. Patient #18 died due to disease progression, so we could not comment on the outcome of PE in this patient. The characteristics, management strategies and the outcomes of patients with PE were summarized in Table 2.

3.4. Generation of pleural effusion and lymphocytosis and response rates

In the PE+ group, the cumulative MMR and CCyR rates under dasatinib at the time of PE generation were 67% and 78%, respectively. Five patients died due to disease progression during the follow-up among patients in PE− group, so these patients were excluded while calculating the response rates. MMR and CCyR rates were significantly lower in PE− group (28% and 33%, respectively) when compared to PE+ patients ($p < 0.05$) (Fig. 1).

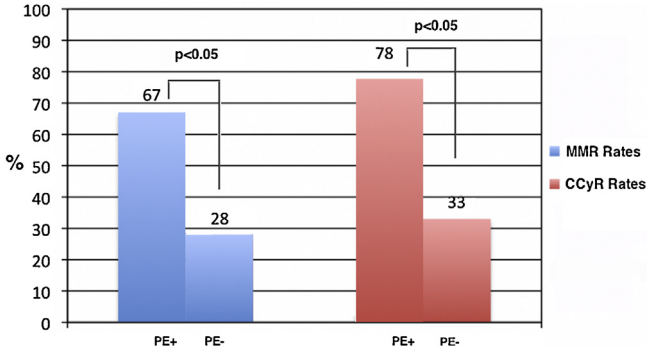

Fig. 1. The MMR and CCyR rates among both patient groups. (PE, pleural effusion; MMR, major molecular response; CCyR, complete cytogenetic response.)

When the entire patient cohort was considered, eight out of 9 patients with lymphocytosis had MMR (89%), whereas this was significantly lower in patients without lymphocytosis (38%) ($p < 0.05$).

3.5. Pleural effusion and survival rates

The PFS was significantly higher in PE+ group than PE− patients ($p = 0.013$) (Fig. 2A). Also the OS was significantly higher among PE+ patients than PE− group ($p = 0.042$) (Fig. 2B). We calculated OS by excluding patients from the both groups with advanced disease at the time of the initiation of dasatinib, and among CP-CML cases, PE+ group had significantly higher OS rate than patients with no PE ($p = 0.024$) (Fig. 3). Among the PE+ patients, PFS and OS did not differ between the cases with or without lymphocytosis $p = 0.490$ (Fig. 4A) and $p = 0.297$, respectively. Also in the PE+ group, PFS and OS were similar between the patients with or without comorbidities ($p = 0.657$ (Fig. 4B) and $p = 0.910$), respectively.

4. Discussion

Dasatinib is a potent second generation TKI, and it is widely used in patients with CML, both in the up-front setting and failure after imatinib. As being an efficacious drug, it inhibits TEC kinases and SFKs, which are responsible for its AEs, so-called "off-target effects" [18].

Clonal expansion of large granular lymphocytes in cases receiving dasatinib therapy has been shown to be associated with pleural

Table 2
Clinical characteristics of patients who developed pleural effusion under dasatinib. (PE, pleural effusion; M, male; F, female; CML, chronic myeloid leukemia; CP, chronic phase; BC, blastic crisis; MMR, major molecular response; CCyR, complete cytogenetic response; NIL, nilotinib, INF, interferon; Ara-C, cytarabine; HU, hydroxyurea; QD, once-daily; BID, twice-daily; HT, hypertension; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CRF, chronic renal failure; IHD, ischemic heart disease.).

Patient #	Age, years/ gender	CML phase at the start of dasatinib	Starting dose of dasatinib, mg/daily/ dosing interval	Comorbidities	Lympho-cytosis (yes/no)	Time of PE gen-eration, months	PE grade	Interruption of dasatinib	Diuretics	Steroids	Outcome of PE	Restart of dasa-tinib	Dasatinib dose at the restart, mg/daily	Alternative treatment for CML	Outcome of CML
1	62/M	CP	100/QD	HT	Yes	12	II	Yes	Yes	Yes	Regression	Yes	70	No	CCyR
2	60/M	CP	100/QD	COPD	No	9	II	Yes	Yes	Yes	Regression	Yes	70	No	CCyR
3	84/F	CP	100/QD	CHF + HT + CRF	No	14	II	Yes	No	No	Regression	Yes	70	No	Died due to BC
4	66/F	BC	140/QD	CHF	No	2	III	Yes	Yes	Yes	Persisting	No	NA	NIL	CCyR
5	42/F	CP	100/QD	None	No	24	III	Yes	Yes	Yes	Regression	Yes	70	No	CCyR
6	51/M	CP	100/QD	None	No	32	I	Yes	Yes	Yes	Regression	Yes	50	No	CCyR
7	53/M	CP	100/QD	None	Yes	18	II	Yes	Yes	Yes	Persisting	No	NA	NIL	CCyR
8	65/F	CP	100/QD	IHD + HT	No	15	II	Yes	Yes	Yes	Regression	Yes	50	No	CCyR
9	39/M	CP	100/QD	None	No	12	II	Yes	Yes	Yes	Regression	Yes	70	No	CCyR
10	57/M	CP	100/QD	None	Yes	20	II	Yes	Yes	Yes	Persisting	No	NA	NIL	CCyR
11	37/F	CP	100/QD	None	Yes	35	I	Yes	No	No	Regression	Yes	50	No	CCyR
12	42/M	BC	100/QD	None	Yes	15	I	Yes	No	No	Regression	Yes	50	No	CCyR
13	58/M	CP	100/QD	None	Yes	3	II	Yes	Yes	Yes	Regression	No	NA	INF/Ara-C[a]	CHR
14	56/M	CP	100/QD	COPD + IHD + HT	No	24	II	Yes	Yes	Yes	Persisting	No	NA	HU[b]	Alive, loss of MMR
15	33/F	CP	100/QD	None	No	4	I	Yes	No	No	Regression	Yes	100	No	CCyR
16	65/F	CP	100/QD	CHF	Yes	16	II	Yes	Yes	Yes	Persisting	No	NA	NIL	CCyR
17	57/F	CP	100/BID	None	No	5	II	Yes	Yes	Yes	Persisting	No	NA	NIL	CCyR
18	56/F	BC	140/QD	None	No	3	II	Yes	Yes	Yes	Unknown	No	NA	NA	Died due to BC

[a] Patient #13 had received up-front nilotinib 2 × 400 mg daily in ENESTnd trial, then shortly after due to grade IV thrombocytopenia, he was switched to imatinib. So after dasatinib, IFN/Ara-C combination was initiated.
[b] This patient had received HU because we cannot administer nilotinib due to prolongation of QTc, and he did not have a suitable donor for allograft.

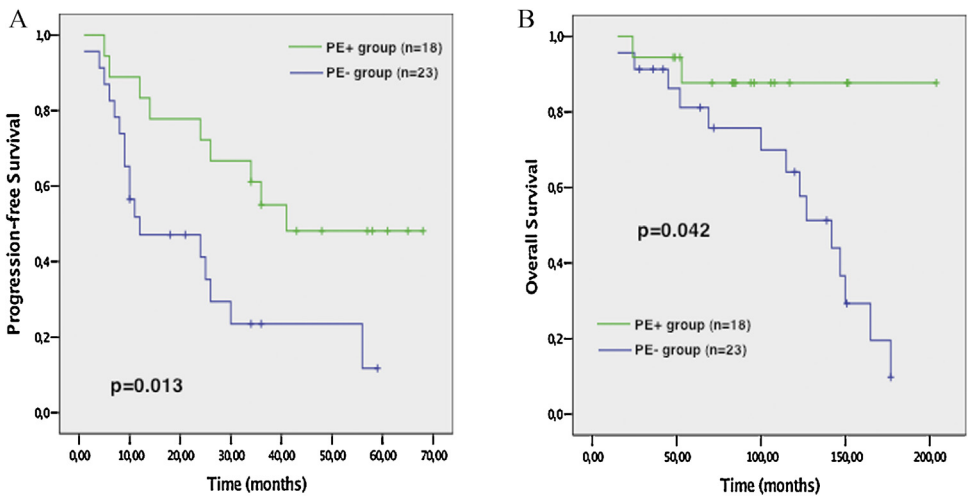

Fig. 2. The progression-free survival (A) and overall survival (B) were significantly higher in PE+ group than PE− patients.

effusion and better outcome [9,10,19]. The mechanism underlying this phenomenon of dasatinib is not clear. The inhibition of SFKs by dasatinib might be the possible reason of this alteration in white blood cell counts [20]. The correlation between the development of lymphocytosis and PE is displayed [8,10], giving a thought that they both might share a common immune-mediated pathogenesis.

PE is frequently seen during dasatinib treatment [11–13,20–22], but the prevalence of PE is highly variable, might differ according to the disease phase, comorbidities, dasatinib dose and/or dose interval, and whether the drug is given first line or subsequently. It is also higher in patients which represent "the real-life data", than reported in clinical trails. For example, among cohorts where usual patient care receiving cases were included, the frequency of PE increases to approximately as high as 40–50% [11,19], especially when used as a second-line treatment, which are consistent with our data of a prevalence of 44%. We previously published a frequency of 43% of PE in patients with CML, when dasatinib was used as a second-line treatment and usual patient care [13].

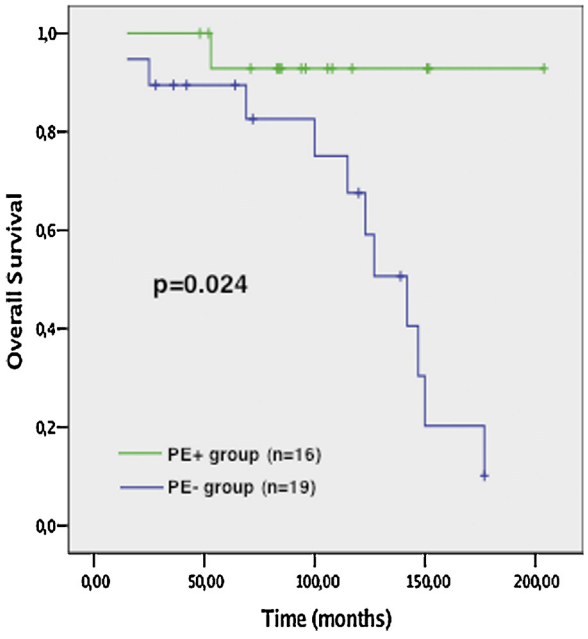

Fig. 3. When only CP-CML cases were taken into account, PE+ group had significantly higher overall survival than patients with no PE.

Although dasatinib is shown to have superior responses in patients with lymphocytosis, this correlation was not strongly shown before in patients with CML who developed PE under dasatinib. Among a cohort of 65 CML patients, event-free survival rate was higher in the PE+ patients when compared with the patients who did not develop PE, but the difference was not significant [11].

Our cohort was equally balanced between two groups regarding gender, risk-stratification, and duration of prior imatinib treatment (Table 1). Patients with an advanced disease at the start of dasatinib were more frequent in PE− group, and as a result of this, the daily mean dosage of dasatinib was higher among those patients.

The dose (i.e. 140 mg vs. 100 mg) or the schedule (100 mg/day, once-daily vs. twice-daily) of dasatinib may result in different results regarding PE generation. Although it has been demonstrated that a higher PE frequency with twice-daily dasatinib administration compared with once-daily dosing was observed in various studies [11,23], this was not the case in our patients. Among our cohort, 30 patients were in CP, of which 28 had started receiving dasatinib 100 mg once-daily. Dasatinib was administered twice-daily in the remaining two patients, in which one had gained PE. In patients with advanced phases, dasatinib 70 mg twice-daily induces a higher incidence of PE than the 140 mg once-daily dose [11,24]. In our cohort, all patients with advanced disease had received dasatinib 140 mg once-daily. This could be the explanation for the low frequency of PE among these patients.

Although the median duration of dasatinib treatment was less than twelve months in some of the previous studies, which described the incidence of dasatinib-related PE [19,20], it has also been demonstrated that as the duration of dasatinib therapy increases, the frequencies of PE may increase [11]. In the study published by Kim et al. [11], dasatinib was administered with a median of 35 months (range, 1–55 months). In the present study the median follow-up period of the entire cohort under dasatinib was 23.5 months, and the median duration of dasatinib therapy of PE+ and PE− groups were 35.5 months and 14 months, respectively. PE could be due to cumulative dosage effect of dasatinib since the median duration of therapy is significantly longer in PE+ cases. Eight of the 18 patients with PE had developed effusions within the first year of follow-up, and in the remaining 10, PEs were observed beyond twelve months of treatment. The median time to effusion generation was fifteen months in PE+ cases, and the patients without an effusion had received dasatinib with a median of 14 months, so it is hard to tell whether some of the PE− patients will develop PE or not, when they will be followed for a longer period of time. Therefore, since PE can be a long-term comorbidity in patients receiving

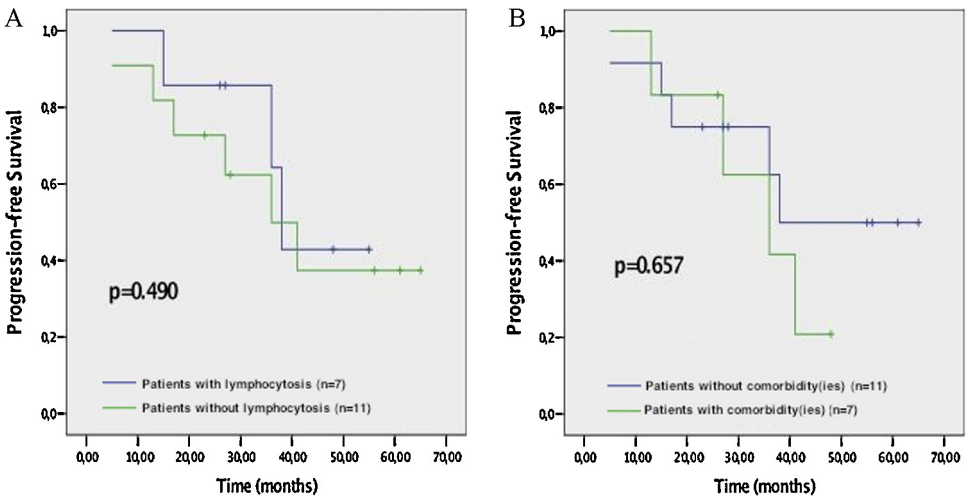

Fig. 4. The progression-free survival was similar between the cases with and without lymphocytosis (A) and patients with or without comorbidities (B) in PE+ group.

dasatinib, the need for close monitoring for longer periods of time may be required.

There are various risk factors that have been identified for PE generation under dasatinib including older age, preexisting cardiac disease, hypertension when the drug was administered as a second-line treatment [20,21,23]. Although the difference was not significant, the median age of PE+ group was higher than patients without PE, and this can be a reason for the high frequency of PEs among these patients. Also the comorbidities were significantly more frequent in the PE+ group, giving an additional explanation for the PE generation.

Lymphocytosis can be observed during dasatinib treatment with different prevalences in different studies varying between 27% and 45% [9,10,19,25–27]. Among our patient cohort, the prevalence of lymphocytosis was 22%, similar to the results displayed in the literature. Patients who develop persisting lymphocytosis tend to have superior response rates [9,10], and among our cases with lymphocytosis the MMR rate was 89%, whereas it was 38% in patients without lymphocytosis. PE can accompany lymphocytosis [8,10], and seven patients with lymphocytosis had also PE, whereas the remaining two cases did not develop effusion ($p < 0.05$).

The MMR and CCyR rates were significantly higher in patients with PE than cases without an effusion. And these responses were durable, for example by continuing with a lower dose of dasatinib (i.e. 50 mg daily), most of the patients maintained their responses without developing PE. Also the PFS and OS were significantly higher in the PE+ group, encouraging us to continue dasatinib in patients with durable responses especially if they develop easily manageable (i.e. grade I/II) PE.

There are several strategies that can be performed in the management of PE, which include dose interruption/reduction and supportive measures, including diuretics and glucocorticoids. Sometimes invasive procedures such as thoracenteses or tube drainage are needed if severe PE is present. Among our cohort, we performed invasive procedures in two patients with grade III PE, in addition to interrupting the drug with administration of diuretics and steroids. In the remaining cases, four of them were switched to nilotinib, and HU was administered in one due to persisting PE, and on patient died due to disease progression, so we could not comment on the outcome of PE. Effusions were fully recovered in the rest of the patients.

To conclude, we displayed that CML patients who developed PE under second-line dasatinib had greater CCyR and MMR rates when compared with cases without an effusion. Also the PFS and OS were significantly higher in PE+ patients than PE− cases. So in patients with grade I/II PE, and durable responses under dasatinib, performing the management strategies for the recovery of effusion, together with continuing dasatinib (if possible) can be a reasonable choice mainly in countries where third generation TKIs are not available. But alternative treatment strategies such as nilotinib or third generation TKIs can be chosen in patients with grade III/IV PE especially if the quality of life is severely affected.

Conflict of interest

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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