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Dasatinib: efficacy, side effects and rôle of comorbidities

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Summary. *Background and aim:* Dasatinib, a dual Abl/Src tyrosine kinase inhibitor, has shown good efficacy in Chronic Myeloid Leukemia treatment, obtaining earlier and deeper response compared to Imatinib, in second and first line. The safety profile of Dasatinib was shown to be acceptable and manageable. In view of the very good clinical results, the issue of baseline comorbidities and their influence on promoting adverse events became relevant. *Materials and methods:* Both second and first line Dasatinib trials showed good efficacy with low toxicity. The most frequent side effects were thrombocytopenia, mainly observed during the first months of treatment, and pleural effusion. *Results:* The majority of side effects were of low grade and manageable with dose adjustments. The pleural effusion rate was 24% at 5-years. It was generally mild to moderate, reversible, manageable; only 5% of pts discontinued treatment due to PE. The median time of appearance is 40 weeks and most of them do not recur. The occurrence of pleural effusion generally do not affect the efficacy of Dasatinib. In the last years the role of comorbidities has been underlined as alert signal to prevent the occurrence of side effects by TKIs. *Conclusion:* A careful work up at diagnosis and during the treatment, other than to implement, in some cases, supportive therapy, would help to prevent the side effects, without neglecting the role of comorbidity that could be not considered as an absolute contraindication to treatment but a warning factor to take in account in the treatment choice.

Key words: Dasatinib, side effects, comorbidity

«Dasatinib: efficacia, effetti collaterali e ruolo delle comorbidità»

Riassunto. *Background e scopo:* Dasatinib, doppio inibitore di Abl e Src chinasi, ha mostrato una buona efficacia nel trattamento della leucemia mieloide cronica, ottenendo risposte più veloci e profonde rispetto ad Imatinib, sia in seconda che in prima linea. Il profilo di sicurezza di dasatinib ha dimostrato di essere accettabile e gestibile. In considerazione degli ottimi risultati clinici, diventa rilevante il tema delle comorbidità alla diagnosi per la loro influenza sugli effetti collaterali del farmaco. *Materiali e metodi:* Sia in seconda che in prima linea Dasatinib ha mostrato buona efficacia con bassa tossicità. Gli effetti collaterali più frequenti sono stati la trombocitopenia, principalmente osservata durante i primi mesi di trattamento, ed il versamento pleurico. *Risultati:* La maggior parte degli effetti collaterali sono stati di basso grado e gestibili con aggiustamenti di dose. La percentuale di versamento pleurico è stato del 29% a 5 anni. In generale, è stato di grado lieve/moderato, reversibile e gestibile; solo il 5% dei pazienti ha interrotto il trattamento a causa del versamento pleurico. Il tempo mediano di comparsa è di 40 settimane, e nella maggior parte dei pazienti non è stato ricorrente. La presenza di versamento pleurico non ha influenzato l'efficacia di Dasatinib. Negli ultimi anni è stato sottolineato il ruolo delle comorbidità come segnale di allerta per prevenire il verificarsi di effetti collaterali da parte dei TKIs. *Conclusioni:* Un attenta anamnesi ed una valutazione delle eventuali comorbidità, oltre che la loro gestione, sia alla diagnosi che durante il trattamento, potrebbe essere utile per prevenire gli effetti collaterali dei TKIs. Le comorbidità potrebbero quindi non costituire una controindicazione assoluta, ma un fattore di allarme da considerare nella scelta del trattamento.

Parole chiave: Dasatinib, effetti collaterali, comorbidità

Introduction

Dasatinib is a potent multikinase inhibitor targeting the SRC family of kinase, receptor kinases, TEC family kinases and with great potency BCR-ABL. The Dasatinib multikinase activity may have therapeutic advantages, in particular in BCR-ABL indipendent mechanisms of resistance in Chronic Myeloid Leukemia. Moreover, Dasatinib seems activate and mobilize anti leukemic immune response, which may improve the efficacy (1).

Dasatinib is active against the majority of clinically relevant Imatinib resistant BCR-ABL mutations, except for T315I and F317L (2).

Dasatinib has been approved for second line treatment after Imatinib resistance and/or intolerance in Chronic Myeloid Leukemia in Chronic Phase (CML-CP)at recommended dose of 100 mg once daily and at 140 mg once daily in advanced phases of disease (accelerated and blast phases) and in Ph+ ALL. Moreover, on the basis of its better efficacy on Imatinib in obtaining faster and deeper molecular responses (3) it has been approved in first line treatment of CML-CP patients at the dose of 100 mg once daily orally. It is administrate with or without meal (4).

Efficacy of Dasatinib

Dasatinib second line trials: good efficacy with low toxicity

After assessing the efficacy of Dasatinib in phase I study (5), a series of phase II studies were performed in CML-CP, CML-AP and CML-BP in second line. In CML-CP Dasatinib induced complete cytogenetic response (CCyR) in 53% of patients. This response was confirmed in the trial in which Dasatinib was randomized versus high-dose Imatinib in patients resistant to standard dose of imatinib (CCyR 44% vs 18%) (3, 6). The phase III dose optimization study showed that the 100 mg once a day dose was associated with similar efficacy as the twice-daily regimen, but with reduction of toxicity (7). Based on the above results, a dose optimization trial started in which patients were randomized to receive Dasatinib at 100 mg once daily, 140 mg once daily, 50 mg twice daily or 70 mg twice daily, respectively. The rates of CCyR and major molecular response (MMR) at 2 years of follow-up were similar across the different dose schedule (CCyR 50-54%, MMR 37-38%). In 100 mg once daily arm, the 2 years rates of overall survival, progression-free survival and transformation to AP/BP were 91, 80 and 3%, respectively. Moreover, this arm was associated with improved safety. In 100 mg once daily arm, the toxicity including all grade of pleural effusion, the most frequent side effect observed, grade> 3 thrombocytopenia, all grade neutropenia and leucopenia, were significatively lower compared with other schedules (8, 9).

These results are updated at six years with similar good results in earlier and deeper response in this setting of CML patients with safe profile . The results show better estimated 6-years rate of overall survival (OS) and progression free survival (PFS) for 100 mg once daily arm (71 and 49%, respectively). Moreover in this arm the MMR was achieved in 43% of patients. In this study too, the achievement of a BCR-ABL $\leq$ 10% at 3 months resulted in long-term benefit. Even the safety profile of Dasatinib 100 mg once daily confirmed a favorable long-term risk profile.(10)

Similar trials in advaced phases of CML, showed, in Dasatinib arm, same better results on response rate with improved safety. The recommended dose of Dasatinib in this setting of patients was 140 mg once daily. (11)

Dasatinib first line in newly diagnosed CML-CP: early and deep responses

The excellent results of second line trial with Dasatinib led to explore the clinical benefit of this drug in the first line setting, on the rationale also that earlier responses were associated to better outcomes (12).

The efficacy and safety of Dasatinib in CML first line is widely confirmed by many trials in newly diagnosed CML-CP patients.

After the phase II open label trial (13), Dasatinib was investigated by a randomized phase III trial (DASISION: DASatinib vs Imatinib Study In Treatment-Naïve CML patients) in which Dasatinib 100 mg once a day was compared to Imatinib 400 mg/day in newly diagnosed CML-CP patients. In this trial Dasatinib showed higher response rate compared to

Imatinib. The cCCyR rate, primary endpoint of the trial, was 77% with Dasatinib and 66% with Imatinib at 12 months; the cumulative MMR rate after 5-year follow-up was 76 and 63% in Dasatinib and Imatinib respectively. The cumulative rates of MR^4 and $MR^{4.5}$ at 5-years were higher for Dasatinib vs Imatinib (65 vs 49 % and 42 vs 33%, respectively). The transformation to AP/BP occurred in lower percentage of patients in Dasatinib arm vs Imatinib arm (4,6 vs 7,3 %, respectively). At 5-years, the progression free survival was 85% in both arms, while overall survival rates were 91 and 90% for Dasatinib and Imatinib, respectively. Moreover, the percentage of patients achieving BCR/ABL transcript ≤ 10% at 5 years was significatively higher for dasatinib than Imatinib (84 vs 64%, p= <.0001), as well as BCR/ABL transcript ≤ 1% at 6mo (69 vs 49%) and BCR/ABL transcript ≤ 0,1% at 12 months (46 vs 30%). Dasatinib was associated with an earlier and higher rate of deeper responses , with lower transformation rates, better long-term outcomes and improved response. After 5 years, no new safety signals have been reported (14).

The SWOG S0325 phase II trial supported the results of DASISION trial. In this trial newly diagnosed CML-CP patient were randomized to receive Dasatinib 100 mg/day vs Imatinib 400 mg/day. Dasatinib arm showed greater frequency of CCyR and MMR (59 vs 44% p=0.059) compared with IMATINIB at 12 months. Overall, progression free survival and event free survival did not differ between the arms. Toxicity profile showed higher incidence of pleural effusion and grade 3/4 thrombocytopenia in the Dasatinib arm, while higher incidence of edema and nausea was seen in Imatinib arm (15).

SPIRIT 2 trial was the largest investigator-conducted randomised trial of Dasatinib 100 mg/day vs Imatinib 400 mg/day in newly diagnosed CML-CP patients in U.K. The primary endpoint of the study was 5 year Event Free Survival.

At 12 months, MR^3 and $MR^{4.5}$ rates were 43 and 5.9% for Imatinib versus 58 and 13.5% for dasatinib, respectively. Both differences in results were statistically significant. Most frequent side effects were pleural effusion and headache for Dasatinib while gastrointestinal events were seen in Imatinib arm. Curiously, the patients who experienced pleural effusion, had better molecular response(16)

Side effects and adverse events

Some adverse events have been reported in patients receiving Dasatinib, including myelosuppression, especially thrombocytopenia, pleural effusion, headache, fatigue, bleending events and, more recently, pulmonary arterial hypertension (PAH). They occurred, generally, in 12-24 months of treatment, were of low grade and manageable with dose adjustments (4).

G3/G4 thrombocytopenia and neutropenia were the most frequent hematological side effects in first and second line, but rarely determine treatment discontinuation. (17, 18)

In second line trials, cytopenia were common but reversible and manageable with dose modifications; pleural effusion occured in 17% of patients and was managed with dose interruption, diuretic or steroid.(17)

In phase III dose-optimization trial it became evident the the 100 mg once a day dose was associated with reduced incidence of pleural effusion and grade 3/4 thrombocytopenia with maintained efficacy. In the last update of this study most adverse events were mild/moderate and occurred by 2 years (9, 10).

In first-line trials the same AEs were observed. In DASISION trial the hematological side effects were represented by neutropenia (25%), thrombocytopenia (20%) and anemia (12%).

The most common non-hematological side effects were myalgia (13%), headache (13%), rush (13%); the pleural effusion (PE) rate was 29% at 5-years. It was generally mild to moderate, reversible, manageable and only 5% of pts discontinued treatment due to PE. The management of this side effect included the dose reduction or interruption of Dasatinib, the use of diuretics or corticosteroid (14, 19).

The occurence of pleural effusion generally do not affect the efficacy of Dasatinib, the median time of appearance is 40 weeks and most of them do not recurr (20, 21).

The management of pleural effusion is an important issue in examining side effect by Dasatinib. It is generally of low grade and reversible if the right therapy is suddenly implemented. The current management suggests treatment with diuretics and steroids and discontinuation as follow: i) grade 2 resume at the same dose of 100 mg once daily at recovery, ii) at event

recur, resume at 80 mg once daily after recovery, iii) after third recurrence, resume at 50 mg once daily after recovery. In severe cases, therapeutic thoracentesis are indicated (4)

The pathogenesis of this particular side effect has not been clearly elucidated. It is likely related at off target kinase inhibition. To date, Dasatinib inhibits PDGFR-B expressed in pericytes and *SRC* (v-src, sarcoma viral oncogene homolog) family of kinases expressed in lymphocytes that regulate vascular permeability (22).

In some patients large granular lymphocyte (LGL) expansion occurs (CD8+ T cytoxic or oligoclonal NK expansion), resulting in peripheral lymphocytosis. It seem that patients with this expansion experiment more frequent pleural effusion, but also better response. The presence of lymphocitosis in patients who showed pleural effusion, suggested that the development of pleural effusion might be an immune-mediated process (23).

More recently rare case of pulmunary arterial hypertension (PAH), defined as the elevation of the mean pulmonary artery pressure, have been reported during Dasatinib treatment, especially in second line. In all these cases the permanent discontinuation of the drug led to an improvement of hemodynamic and clinical parameters (24-28). In DASISION trial the incidence of PAH was 3% (8 on 258 patients).Right heart catheterization(RHC) required for diagnosis, was performed in 1 patient and did not confirm pulmonary arterial hypertension. Only one patient discontinued Dasatinib treatment as results of PAH (29).

Dasatinib and comorbidity

Dasatinib demonstrated superiority over imatinib in the treatment of CML patients, obtaining faster and deeper responses with better PFS and better long-term outcome in both first and second line. In view of the very good clinical results, become important the issue of baseline comorbidities and their influence on promoting adverse events in CML patients.

Comorbidity is, by Feinstein definition (30), any distinct additional clinical entity pre-existing or occurring during the course of a primary disease. A large retrospective database of more than 1800 CML patients reported that 88% of these had more than one comorbidity at baseline and 63% of patients assumed more than 1 drug not CML related (31).

At diagnosis, the role of comorbidities on drug adverse event profile, is to be considered not only for making the final choice, but also for taking care of patients during treatment. Therefore, it would be useful to perform a depth work up for pointing out the presence and, if already known, the severity of comorbidities to avoid adverse events. In figure 1 there is an example of a possible work-up schedule for CML patients at diagnosis and during the treatment. Most TKIs in fact are reasonably well tolerate, when adequate monitoring and supportive care are in place, using specific laboratory tests, instrumental procedures (e.g. echocolordoppler) and specific SCORE chart (e.g. European Society of Cardiology score chart), as suggest by some authors (32).

In 2010, a sub analysis of DASISION study on the impact of baseline comorbidity, excluding cardiovascular comorbidities, on safety and efficacy of the treatment, showed that the presence of baseline comorbidities appeared to have no effect on the safety and efficacy of either Dasatinib or Imatinib as initial therapy for CML-CP (33).

The event that have most impact on Dasatinib adverse event profile, is pleural effusion. In the majority of cases, it responds to a temporary drug discontinua-

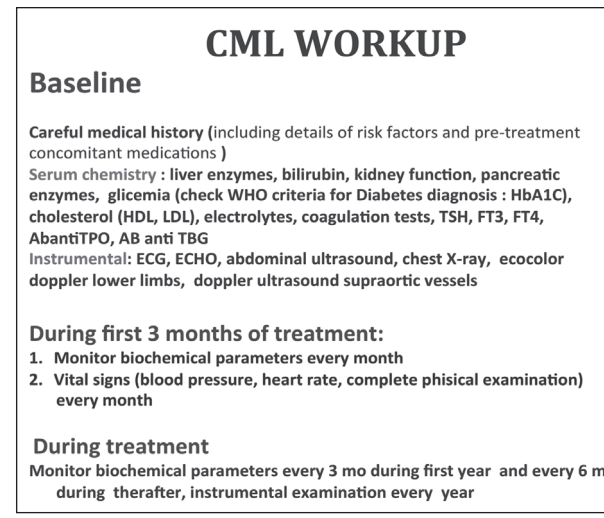

Figure 1. Suggested CML Work up in the management of CML patients at diagnosis and during treatment with TKIs.

tion with short course of corticosteroids and diuretics and, usually, do not recur after resuming the drug at a lower dose (20, 33).

Some risk factors as hypertension, prior cardiac history, female sex, age > 65ys, twice-daily schedule, autoimmune disorders, history of skin rush were identified (34-36).

The pleural effusion might be relevant for patients with a history of severe lung disease (e.g., chronic obstructive pulmonary disease), severe cardiac disease (e.g., congestive heart failure) or uncontrolled hypertension. In this condictions as well as in more moderate ones (controlled hypertension, moderate lung diseases or not severe cardiac diseases), a careful workup at diagnosis and during the follow-up might help the management of the patients, resulting in a rapid establishment of therapy.

In DASISION trial the treatment was well tolerate in both arm; most adverse events occuring within the first 2 years. Only pleural effusion showed a minimal increase on each years of treatment. Therefore it is important to follow the patients more strictly during first years of treatment to prevent the side effects, expecially performing cardiac and respiratory monitoring. It would be useful to add some farmacological supports and suggest to the patient to report any new respiratory symptom during Dasatinib treatment. Intermittent use of loop diuretics may helps to minimize fluid retention, especially if patients have significant risk factors.

Pulmonary arterial hypertension (PAH) is a rare adverse event reported during dasatinib treatment (24-28). The pathogenesis of this adverse event is unclear , perhaps related to off-target kinase inhibition, causing pulmonary vascular smooth muscle cell changes and pulmunary vascular resistance increase. Echocardiography has acceptable accuracy for use as the initial measure of pulmonary pressures in evaluating patients in whom PH is suspected, but it is not sufficient to diagnose PH without RHC (37). The patients with preexisting PAH may be considered for alternative TKIs in the frontline setting. Instead, patients with other cardiopulmonary conditions have to be followed more closely with clinical and instrumental procedures.

The role of comorbidities in elderly patients might be considerable not only for severity in itself but also for frequent additional treatment.

In Imatinib treated elderly patients comorbidities appeared to have an impact on median OS (40.8 vs 20.16 months for patients with Charlson comorbidity index score 0 vs ≥1, respectively), EFS and non-CML death rate (38).

In a subanalysis of the DASISION study, the safety profile of dasatinib was similar across age groups (younger than 46 vs 46-65 vs older than 65 years) showing that the age is not a limiting factor in this setting of patients treated with Dasatinib (32). In another study, 125 unselected patients with CP-CML aged >60 years resistant/intolerant to imatinib treated with Dasatinib, were retrospectively evaluated. Also in this setting of patients, Dasatinib, at the recommended dose of 100 mg/day, proved to be effective and safe (39).

Thus it is important to perform an appropriate screening for comorbidities at diagnosis and to follow the patients during the treatment with a careful work up to prevent or to treat as soon as possible the side effect to avoid the possibility of a persistent adverse event. It should be reminded that we are treating a chronic patient with a chronic disease and the tolerability profile is an important issue. In this context, the comorbidities should not be seen as an absolute controindication but only a warning factor to follow and manage the patients in the best way.

Conclusion

Treatment success in CML depend in large part on compliance, effective management of side effects and close monitoring to achieve cytogenetic and molecular milestones. In this way, it is important to choice the best effective therapy because we have to take care of a manageable but neoplastic disease. Dasatinib has shown good efficacy giving earlier and deeper responses in first and second line treatment, with reasonable safety profile and manageable side effects. The presence of comorbidities should be considered as a warning risk factor but not as an absolute controindication to treatment. Performing a careful work up at diagnosis and during the treatment, other than to implement in some cases supportive therapy, would help to prevent the side effects and the adverse event of the therapy.

References

1. Shah NP, Tran C, Lee FY, *et al.* Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004; 305: 399-401.
2. Branford S, Melo JV, Hughes TP. Selecting optimal secondline tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABLmutation status really matter? Blood 2009; 114: 5426-35.
3. Hochhaus A, Kantarjian HM, Baccarani M, *et al.* Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. Blood 2007; 109: 2303-9.
4. European Medicines Agency Sprycel (dasatinib) 2014 [summary of product characteristics]. Bristol-Myers Squibb Pharma EEIG, Uxbridge, UK.
5. Talpaz M, Shah NP, Kantarjian H, *et al.* Dasatinib in imatinibresistant Philadelphia chromosome-positive leukemias. N Engl J Med 2006; 354: 2531-41.
6. Kantarjian H, Pasquini R, Lévy V, *et al.* Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R).Cancer 2009; 115 (18): 4136-47.
7. Shah NP, Kantarjian HM, Kim DW, *et al.* Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic phase chronic myeloid leukemia. J Clin Oncol 2008; 26: 3204-12.
8. Shah NP, Kim DW, Kantarjian H, *et al.* Potent, transient inhibition of BCR–ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica 2010; 95: 232-40.
9. Shah NP, Kantarjian H, Kim DW, *et al.* Six-year follow-up of patients (pts) with imatinib-resistant or -intolerant chronic-phase chronic myeloid leukemia receiving dasatinib. J Clin Oncol 2012 abstract 6506.
10. Shah NP, Guilhot F, Cortes JE, *et al.* Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. Blood 2014; 123: 2317-24.
11. Saglio G, Hochhaus A, Goh YT, , *et al.* Dasatinib in imatinibresistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. Cancer 2010; 116: 3852-61.
12. Marin D, Milojkovic D, Olavarria E, *et al.* European LeukemiaNet criteria for failure or suboptimal response reliably identify patients with CML in early chronic phase treated with imatinib whose eventual outcome is poor. Blood 2008; 112: 4437–44.
13. Cortes JE, Jones D, O'Brien S, *et al.* Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. J Clin Oncol 2010; 28: 398-404 .
14. Cortes JE, Saglio G, Baccarani M, *et al.* Final Study Results of the Phase 3 Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056). Blood 2014; abs 152.
15. Radich JP, Kopecky KJ, Appelbaum FR, *et al.* A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. Blood 2012; 120: 3898-905.
16. O'Brien S, Hedgley C, Adams S, *et al.* Spirit 2: an NCRI randomized study comparing Dasatinib with Imatinib in patients with newly diagnosed CML. Blood 2014; abs 517.
17. Hochhaus A, Kantarjian H. The development of dasatinib as a treatment for chronic myeloid leukemia(CML): from initial studies to application in newly diagnosed patients. J Cancer Res Clinb Oncol 2013; 139: 1971-84.
18. Breccia M, Alimena G. Occurrence and current management of side effects in chronic myeloid leukemia patients treated frontline with tyrosine kinase inhibitors. Leuk Res 2013; 37; 713-20.
19. Kantarjian H, Shah NP, Cortes JE, *et al.* Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood 2012; 119: 1123-9.
20. Porkka K, Khoury HJ, Paquette RL, , *et al.* Dasatinib 100 mg once daily minimizes the occurrence pleural effusion in patients with chronic myeloid leukemia in chronic phase and efficacy in unaffected in patients who develop pleural effusion. Cancer 2010; 116: 377-86.
21. Laneuville P, Baccarani M, Cortes JE, *et al.* Analysis of patients(pts) with chronic-phase chronic myeloid leukemia (CML-CP) who develop pleural effusion on first-line dasatinib: management and outcomes. J Clin Oncol 2011; 29 abs 6605.
22. Giles FJ, O' Dwyer M, Swords R. Class effects of tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. Leukemia 2009; 23: 1698-707.
23. Schiffer CA, Cortes JE, Saglio G, *et al.* Lymphocytosis following first-line treatment for CML in chronic phase with dasatinib is associated with improved responses: a comparison with imatinib. [abstract 358]. Blood 2010; 116.
24. Nagata Y, Ohashi K, Fukuda S, *et al.* Clinical features of dasatinib-induced large granular lymphocytosis and pleural effusion. Int J Hematol 2010; 91: 799-807.
25. Dumitrescu D, Seck C, ten Freyhaus H, *et al.* Fully reversible pulmonary arterial hypertension associated with dasatinib treatment for chronic myeloid leukemia. Eur Respir J 2011; 38: 218-20 .
26. Montani D, Bergot E, Gunther S, *et al.* Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012; 125: 2128-37 .
27. Hennigs JK, Keller G, Baumann HJ, *et al.* Multi tyrosine kinase inhibitor dasatinib as novel cause of severe pre-

capillary pulmonary hypertension? BMC Pulm Med 2011; 11: 30.
28. Sano M, Saotome M, Urushida T, *et al.* Pulmonary arterial hypertension caused by treatment with dasatinib for chronic myeloid leukemia -critical alert-. Intern Med 2012; 51: 2337-40.
29. Jabbour E, Kantarjian HM, Saglio G, , *et al.* Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). Blood 2014; 123: 494-500.
30. Feinstein AR. The pre-therapeutic classification of comorbidity in chronic disease. J Chronic Dis 1970; 23: 455-68.
31. Breccia M, Alimena G. The role of comorbidities in chronic myeloid leukemia. Leuk Res, 2013; 37: 729-30.
32. Breccia M, Molica M, Zacheo I, , *et al.* Systematic Coronary Risk Evaluation (SCORE) Chart Identify Chronic Myeloid Leukemia Patients at Risk of Cardiovascular Diseases during Nilotinib Treatment. Blood 2014; abs 4545.
33. Khouri HJ, Cortes EJ, Kantarjian H, , *et al.* Safety and efficacy of Dasatinib (DAS) vs Imatinib by baseline comorbidity in patients with Chronic Myeloid Leukemia in chronic phase: analysis of the Dasion trial. Blood 2010; 116 abs 3421.
34. Quinta's-Cardama A, Kantarjian H, O'brien S, *et al.* Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. J Clin Oncol 2007; 25: 3908-14.
35. Porkka K, Khoury HJ, Paquette RL, *et al.* Dasatinib 100 mg once daily minimizes the occurrence of pleural effusion in patients with chronic myeloid leukemia in chronic phase and efficacy is unaffected in patients who developpleural effusion. Cancer 2010; 116: 377-86 .
36. Breccia M, Alimena G Pleural/pericardic effusions during dasatinib treatment: incidence, management and risk factors associated to theur development. Expert Opin Drug Saf 2010; 9: 713-21.
37. Galiè N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009; 34: 1219-63.
38. Breccia M, Luciano L, Latagliata R, *et al.* Age influences initial dose and compliance to imatinib in chronic myeloid leukemia elderly patients but concomitant comorbidities appear to influence overall and event-free survival. 2014; 38 (10): 1173-6.
39. Latagliata R, Breccia M, Castagnetti F, *et al.* Dasatinib is safe and effective in unselected chronic myeloid leukaemia elderly patients resistant/intolerant to imatinib. Leuk Res 2011; 35: 1164-9.

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