Citation: Nielsen P, Engelhardt R, Grosse R, Janka G, Harmatz P, Fischer R. Italian Society of Hematology Guidelines for thalassemia and non-invasive iron measurements. Haematologica 2009; 94:294-295. doi: 10.3324/haematol.13600

References

1. Angelucci E, Barosi G, Camaschella C, Cappellini MD, Cazzola M, Galanello R, et al. Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders. Haematologica 2008;93:741-52.
2. Brittenham GM, Farrell DE, Harris JW, Feldman ES, Danish EH, Muir WA, et al. Magnetic-susceptibility measurement of human iron stores. N Engl J Med 1982;307:1671-5.
3. Piga A, Fischer R, Harmatz P, St. Pierre TG, Longo F, Fung E, et al. Comparison of LIC obtained from biopsy, BLS and R2-MRI in iron overloaded patients with β-thalassemia, treated with deferasirox (Exjade, ICL670). Blood 2005;106: 755a.
4. Fischer R, Farrell D. Liver iron susceptometry. In: Andrew M, Nowak H, editors. Magnetism in Medicine: a handbook, completely revised and extended edition. Berlin: Wiley-VCH; 2007. p. 529-49.
5. Carneiro AAO, Fernandes JP, De Araujo DB, Elias J, Martinelli ALC, Covas DT, et al. Liver iron concentration evaluated by two magnetic methods: magnetic resonance imaging and magnetic susceptometry. Magn Reson Med 2005;54:122-8.
6. Fischer R, Harmatz P, Nielsen P. Does liver biopsy overestimate liver iron concentration? Blood 2006:108:1775-6; author reply 1776.
7. Fischer R, Engelhardt R, Nielsen P, Gabbe EE, Heinrich HC, Schmiegel WH, et al. Liver iron quantification in the diagnosis and therapy control of iron overload patients. In: Hoke M, Erne SN, Okada YC, Romani GL, editors. Biomagnetism: clinical aspects. Amsterdam: Elsevier; 1992. p. 585-8.
8. Ropert-Bouchet M, Turlin B, Graham G, Rabault B, Le Treut A, Brissot P, et al. Drying methods affect the wet:dry weight ratio of liver tissue samples and impact liver iron content (LIC) measurements. In: First Congress of the International BioIron Society; 2005 May 25. Prague, Czech Republic.
9. Pakbaz Z, Fischer R, Vichinsky E, Fagaly RL, Paulson DN, Pratt K, et al. Liver iron measurement by SQUID biosusceptometry compared to liver biopsy: a more accurate definition of optimal iron range. Blood 2007;106:786a.
10. Engelhardt R, Langkowski JH, Fischer R, Nielsen P, Kooijman H, Heinrich HC, et al. MRI-sequences for liver iron quantification: studies in aqueous iron solutions, iron overloaded rats and patients with hereditary hemochromatosis. Magn Reson Imag 1994;12:999-1007.
11. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with β-thalassemia. Blood 2006;107:3455-62.
12. Pakbaz Z, Fischer R, Fung EB, Nielsen P, Harmatz P, Vichinsky E. Serum ferritin underestimates liver iron concentration in transfusion independent thalassemia patients as compared to regularly transfused thalassemia and sickle cell patients. Pediatr Blood Cancer 2007;49:329-32.

Italian Society of Hematology guidelines for thalassemia and non-invasive iron measurements: author reply

We greatly appreciated the comments of Dr Nielsen and colleagues on the guidelines for the management of iron overload in thalassemia we produced on behalf of the Italian Society of Hematology.[1] Dr Nielsen and colleagues are concerned about our interpretation of data regarding the accuracy of biomagnetic liver susceptometry (BLS) as a non-invasive method for assessing liver iron concentration. By analyzing the existing evidence, we relied on the only two references dealing with a correlation between BLS and liver iron concentration by biopsy in patients with thalassemia. Our conclusion on the inaccuracy of BLS was mainly grounded on a paper published as an abstract by Piga *et al.*[2] in which the sentence "*on average, the LIC data obtained from BLS and biopsy were related by a factor of 0.46*" was interpreted as 0.46 being the correlation coefficient of the two measurements. Thus, from this factor, we derived a R^2 of 0.21. We also relied on the conclusion of the abstract that states "*overall, LIC from biopsy was generally larger than that obtained from BLS*".

Regarding the use of SQUID/BLS after the first study published by Gary Brittenham in 1982,[3] no other published study has confirmed the capability of SQUID to predict hepatic iron concentration with adequate methods. Any validation study of a new diagnostic quantitative procedure must compare the new methodology with a reference *gold* standard. Particularly a determination coefficient (R^2) with a prediction interval (95% CI) should be reported.

Above all in this specific case the 95% prediction interval would be reasonably narrow not extending over the identified threshold for iron concentration tissue damage and death risk.[4] In the setting of iron overload, the reference standard is the validated biochemical determination of hepatic iron concentration on adequate, non cirrhotic, liver biopsy specimens.[5] We are not aware of any such study with results similar to that reported by Dr Brittenham with a similar 95% confidence prediction interval. Studies comparing SQUID/BLS with other technologies are of minor relevance. Moreover the cited debate on dry weight-wet weight relationship developed after an industry sponsored trial,[2] which, although important for future development, raises concern for the thousands of determinations performed for clinical practice before 2006.

In conclusion, although SQUID/BLS is a highly scientific methodology, because of the limited availability, the limited literature in peer reviewed journals, the reported difficulties, and the availability of other non-invasive methods (MRI-R2) it appears rational to recommend its utilization only inside clinical trials.

Emanuele Angelucci,[1] Giovanni Barosi,[2] Monia Marchetti,[2] and Sante Tura[3]

[1]Hematology Department and BMT Unit, Cancer Center "Armando Businco", Cagliari; [2]Laboratory of Clinical Epidemiology, Fondazione IRCCS Policlinico S. Matteo, Pavia; [3]Istituto di Ematologia ed Oncologia Medica "Seragnoli", Università di Bologna, Italy.

Key words: clinical practice guidelines, systematic review, thalassemia major, SQUID, biomagnetic liver susceptometry..

Correspondence: Emanuele Angelucci, MD. Hematology Department and BMT Unit, Cancer Center "Armando Businco", via Edward Jenner, 09121 Cagliari, Italy. E-mail: emnang@tin.it

Citation: Angelucci E, Barosi G, Marchetti M, and Tura S. Italian Society of Hematology guidelines for thalassemia and non-invasive iron measurements: author reply. Haematologica 2009; 94:295-296. doi: 10.3324/haematol.2008.001651.

References

1. Angelucci E, Barosi G, Camaschella C, Cappellini MD, Cazzola M, Galanello R, et al. Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders.

Haematologica 2008;93:741-52.
2. Piga A, Fisher R, Harmatz P, St. Pierre TG, Longo F, Fung E, et al. Comparison of LIC obtained from biopsy, BLS and R2-MRI in iron overloaded patients with β-thalassemia, treated with deferasirox (Exjade, ICL670). Blood 2005; 106:755a.
3. Brittenham GM, Farrell DE, Harris JW, Feldman ES, Danish EH, Muir WA, et al. Magnetic-susceptibility measurement of human iron stores. N Engl J Med 1982;307:1671-5.
4. Olivieri NF. The {beta}-Thalassemias. N Engl J Med 1999;341:99-109.
5. Angelucci E, Brittenham GM, McLaren CE, Ripalti M, Baronciani D, Giardini C, et al. Hepatic iron concentration and total body iron stores in thalassemia major. N Engl J Med 2000;343:327-31.

Effective use of imatinib-mesylate in the treatment of relapsed chronic myeloid leukemia after allogeneic transplantation

Despite recent advances in the treatment of chronic myeloid leukemia (CML), allogeneic stem-cell transplantation (SCT) remains the only curative option. The success of SCT is limited because of relapse in 20-30% of patients.[1,2] As the graft-versus-leukemia (GvL) effect contributes to cure, the cessation of immunosuppression[3] and use of donor lymphocyte infusions (DLI)[4] have become established treatment for relapse. DLI is most effective if given for molecular or cytogenetic relapse. However, GvHD is increased if used in the first year post-transplant. Other options include interferon α (IFN) or a second transplant.

Imatinib mesylate (IM) is a potent inhibitor of the BCR-ABL tyrosine kinase and achieves complete cytogenetic responses (CCR) in 87% of previously untreated patients.[5] More recently its role in relapse after SCT has been highlighted.[6,7] We describe the use of imatinib in 14 patients who relapsed post-SCT and were subsequently treated with IM.

All patients with Ph-positive CML in first chronic phase (CP) who relapsed (n=14) following an allogeneic transplant performed between 1987 and 2004 are included. There were 7 males and 7 females. The median age at diagnosis was 31 years (range 15-48) (Table 1). Pre-transplant treatment included either hydroxycarbamide (OHU) and/or IFN. All patients were IM naïve at the time of transplant and were transplanted in CP, 13 using a matched sibling donor and one a matched unrelated donor.

The conditioning regimen was Bu/Cy (9 patients) or Cy/TBI (5 patients). All the transplants were T-cell replete and cyclosporine and methotrexate were used as GvHD prophylaxis. Four patients developed acute GvHD limited to the skin and were treated with corticosteroids. Follow-up included clinical evaluation, blood counts, bone marrow examination including morphology and cytogenetics. From 2002, patients were monitored by qualitative, nested BCR-ABL RT-PCR and if positive, had BCR-ABL transcript levels determined by real-time quantitative PCR (RQ-PCR). Patients were deemed to have had a molecular relapse if greater than a five-fold increase in BCR-ABL transcript levels was observed.

Median time to first relapse was 36 months (range 7-180) (Table 2). Prior to the availability of IM, 4 patients received DLI at incremental doses with only one patient showing any durable response. The other 3 patients proceeded to a reduced intensity-conditioning transplant with short responses before relapsing (Patients 2, 7 and 9 in Table 2). At the time of introduction of IM, 10 patients were in their first relapse and 4 patients were in second relapse. Four patients had a hematologic [3 CP and one accelerated phase (AP)] relapse, 4 had a cytogenetic relapse and the remaining 6 had a molecular relapse. Imatinib was started at a dose of 400 mg daily in all patients except the patient with AP disease who received 600 mg daily.

Table 1. Pre-transplant.

Case#	Age at diagnosis	Rx before BMT	Time to transplant days	EBMT risk score	Conditioning	Type of transplant
1	35	OHU[1]	372	2	Cy / TBI	Sib-Allo
2	48	OHU	402	3	Bu / Cy	Sib-Allo
3	45	OHU	334	2	Bu / Cy	Sib-Allo
4	21	OHU/IFN	207	1	Cy / TBI	Sib-Allo
5	15	OHU	447	0	Bu / Cy	Sib-Allo
6	32	OHU/IFN	502	2	Bu / Cy	Sib-Allo
7	36	OHU	152	1	Bu / Cy	Sib-Allo
8	40	OHU/IFN	170	2	Bu / Cy	Sib-Allo
9	25	OHU	731	2	Cy / TBI	Sib-Allo
10	15	OHU/IFN	503	2	Cy / TBI	MUD
11	30	IFN	847	2	Bu / Cy	Sib-Allo
12	28	OHU	2227	1	Bu / Cy	Sib-Allo
13	25	Bu/Thiogua	948	2	Cy / TBI	Sib-Allo
14	30	OHU / IFN	334	2	Bu / CY	Sib-Allo

[1] *Oxyhydroxyurea.*

Thirteen (93%) patients responded to IM with a median time to response of four months (range 3-15). Of the 4 patients treated in hematologic relapse, 2 achieved a CCR and became nested PCR negative (<1 BCR-ABL transcripts in 105). The other 2 patients had transient responses before developing progressive disease. Of the 10 patients who were treated for cytogenetic or molecular relapses, all achieved a CCR and 9/10 became nested BCR-ABL PCR negative.

When these patients were started on IM, there was no data to indicate whether the molecular remissions achieved would be durable or whether these patients should be maintained indefinitely on therapy. Imatinib was stopped in 7 of the surviving 12 patients. The median duration of treatment for patients who stopped IM was 11 months (range 6-35). No patient stopped the drug because of toxicity. Only 2 of the 7 patients who stopped IM have remained in molecular remission with a median follow-up of 42 months. The other 5 patients all had re-emergence of BCR-ABL transcripts. One patient has stable low levels of transcripts and has not received any further treatment. Four patients were restarted on IM, one has again become PCR negative. The remaining 3 patients received DLI in combination with IM, one remains in molecular remission and 2 have low level stable BCR-ABL transcripts and remain in CCR. Five patients were continued on IM: 4 of these patients remain disease free while one has low level stable BCR-ABL transcripts.

DLI is an effective treatment for patients relapsing after SCT for CML and can restore durable molecular remissions in a high percentage of patients.[4,8,9] However, a significant proportion of patients are unresponsive. Toxicity