

Body mass index does not impact on molecular response rate of chronic myeloid leukaemia patients treated frontline with second generation tyrosine kinase inhibitors

Excessive body weight, typically considered as a body mass index (BMI) greater than 25 kg/m² of body surface area according to the World Health Organization classification (Finucane *et al*, 2011), has been associated with a higher risk of cancer development, including breast cancer in women and esophageal, colon, pancreatic, endometrial and kidney cancers in both genders (Bianchini *et al*, 2002). Obesity has also been correlated with the onset of haematological malignancies (Soderberg *et al*, 2009). The relative risk of developing leukaemia has been reported to be 1.14 for overweight (BMI 25- < 30 kg/m²) and 1.39 for obese (BMI ≥30 kg/m²) individuals (Larsson & Wolk, 2008). Research from the MD Anderson Cancer Center has suggested that obesity and adulthood weight gain may increase the risk of developing chronic myeloid leukaemia (CML) (Strom *et al*, 2009). In 2012, our group reported that CML patients with an increased BMI (>25 kg/m²) at diagnosis who received imatinib showed a significantly longer median time to obtain a complete cytogenetic response (CCyR, 6.8 months vs. 3.3 months, *P* = 0.001) and a reduced rate of major molecular response (MMR, 77% vs. 58% *P* = 0.01), which was also achieved over a longer median time (29 months vs 14 months, *P* = 0.01) compared to patients with a lower BMI (Breccia *et al*, 2012). We suggested that having a higher BMI at diagnosis might be considered a risk factor in terms of response achievement and time of response to treatment in CML patients treated with imatinib frontline. The present study was designed to assess the rate of response in a cohort of chronic phase CML patients treated upfront with second-generation tyrosine kinase inhibitors (TKIs) according to BMI at diagnosis. Seventy-eight patients diagnosed between May 2007 and October 2016 at our centre - 53 treated with nilotinib and 25 with dasatinib - entered this analysis. BMI was defined as the body mass divided by the square of the body height, universally expressed in kg/m². According to the BMI, patients were classified into 4 subsets: underweight (<18.5), normal weight (>18.5-<25), overweight (>25-<30) and obese (>30). In our cohort, 40 patients (51.3%) were categorized as underweight/normal weight, while 38 (48.7%) were classified as overweight/obese. Median age at diagnosis was 56 and 55 years for the two subsets of patients, respectively (*P* = not significant). A correlation was identified between increased BMI and gender, with a higher percentage of males being overweight/obese compared to females (68%

vs. 42%, *P* = 0.01). We found no statistically significant association between BMI and prognostic risk stratifications at diagnosis [European Treatment and Outcome Study (EUTOS), Sokal, Hasford and EUTOS long-term survival scores]. Two patients died of CML progression after having developed an *ABL1* T315I mutation, both belonging to the underweight/normal weight group (Table I). All patients were followed according to the 2013 European LeukaemiaNet (ELN) recommendations (Baccarani *et al*, 2013). We assessed the cytogenetic and molecular responses at 3 months and at

Table I. Clinical and biological features at baseline according to BMI.

BMI	<18.5	18.5-<25	>25-30	>30	<i>P</i> -value
Patients, <i>n</i>	1	39	30	8	
Median age (years)	37.3	56	55	47	ns
Gender					
Male	/	16	21	5	0.01
Female	1	23	9	3	
Sokal score					
Low	1	18	17	6	ns
Intermediate	/	17	10	1	
High	/	4	3	1	
EUTOS score					
Low	1	34	29	7	ns
High	/	5	1	1	
Hasford score					
Low	1	21	19	4	ns
Intermediate	/	17	8	3	
High	/	1	3	1	
EUTOS long-term survival score					
Low	1	27	27	6	ns
Intermediate	/	10	2	2	
High	/	2	1	/	
Type of transcript					
b2a2	/	9	10	3	ns
b3a2	1	30	16	5	
b2a2 and b3a2	/	/	4	/	
Type of second generation TKI					
Nilotinib	/	24	22	7	
Dasatinib	1	15	8	1	
Death for CML	/	2	/	/	

BMI, body mass index; CML, chronic myeloid leukaemia; EUTOS, European Treatment and Outcome Study; ns, not significant; TKI, tyrosine kinase inhibitor.

Table II. Cumulative incidences of responses according to BMI.

	BMI <18.5–25	BMI >25– >30	P-value
CCyR rate (%) at 3 months	97.5	100	0.32
EMR rate (%) at 3 months	92.4	94.7	0.68
MMR rate (%) at 3 months	52.5	42.1	0.35
Response rate (%) according to ELN (2013)* at 3 months			
Optimal	92.5	94.7	0.68
Warning	7.5	5.3	
Failure	/	/	
MMR rate (%) at 12 months	75.7	85.3	0.32
Response rate (%) according to ELN (2013)* at 12 months			
Optimal	75.7	85.3	0.32
Warning	18.1	11.8	
Failure	6.1	2.9	
MMR rate (%) after median follow-up of 40 months	35	28.9	0.56
MR4.0† rate (%) after median follow-up of 40 months	22.5	28.9	0.51
MR 4.5‡ rate (%) after median follow-up of 40 months	30	23.7	0.62

BMI, body mass index; CCyR, complete cytogenetic response; DMR, deep molecular response; ELN, European LeukaemiaNet; EMR, early molecular response; MMR, mayor molecular response; MR, molecular response.

*Baccarani *et al* (2013).

†MR 4.0 = *BCR/ABL1* value \leq 0.01%.

‡MR 4.5 = *BCR/ABL1* value \leq 0.0032%.

12 months, and the best molecular response achieved comparing the underweight/normal weight group and the overweight/obese group. At 3 months, there were no significant differences in CCyR rate between patients with lower BMI (<25) and higher BMI (>25) (97.5% vs. 100%; $P = 0.32$). Early molecular response (EMR or a *BCR-ABL1/ABL1* ratio \leq 10% at 3 months), MMR (*BCR-ABL1/ABL* ratio \leq 0.1%) and deep molecular response (DMR, corresponding to MR4 or MR4.5) rates, were not statistically different when comparing the two subsets of patients (Table II). According to the ELN 2013 guidelines, an optimal response was achieved in 92.5% of patients with a lower BMI (<25 kg/m²) and in 94.7% of patients with a BMI higher than 25 kg/m² ($P = 0.68$), while a warning response was seen in 7.5% and 5.3% of patients, respectively ($P = 0.56$). The results were similar at 12 months of treatment for MMR (75.7% vs. 85.3%, $P = 0.32$) and DMR (45.4% vs. 50%, $P = 0.50$), but were always non-significant between the two groups (Table II). According to the ELN 2013 guidelines, 6.1% of underweight/normal weight and 2.9% of overweight/obese patients were considered as failures to second-generation TKI treatment ($P = 0.32$). Finally, we assessed the cumulative incidence of molecular responses achieved after a median follow-up of 40 months. Again, no differences were found in terms of MMR rate (35% vs. 28.9% $P = 0.56$), MR4.0 (22.5% vs. 28.9%, $P = 0.51$), MR4.5 rate (30% vs. 23.7%, $P = 0.62$) for underweight/normal weight and overweight/obese patients, respectively (Table II). Two patients achieved a MR 5.0 (*BCR-ABL1/ABL1* ratio \leq 0.001%) as their best molecular response during the treatment, both belonging to the overweight/obese group.

To our knowledge, this is the first analysis that considers the prognostic impact of BMI on treatment response in CML patients who received second-generation TKIs as frontline therapy. It has been previously hypothesized that imatinib, through the inhibition of *PDGFRA* and *PDGFRB*, may alter the normal signalling regulation of macrophages on pre-adipocytes stimulating adipogenesis (Yarmo *et al*, 2007) and that this interaction might explain the delayed and low rate of molecular responses observed with this drug as frontline treatment. On the contrary, we did not find any significant difference in molecular response between patients with low (<25) and high (>25) BMI who received nilotinib or dasatinib as frontline treatment. The high selectivity and potency of nilotinib and dasatinib (Jabour, 2016) against *BCR/ABL1* and the lower inhibition of *PDGFRA* and *PDGFRB*, with a consequent lower adiponectin differentiation, may explain the similar response rates observed in underweight/normal weight and overweight/obese patients to second generation TKIs. Our results suggest that assessment of BMI at baseline should be considered as a decision factor prior to starting treatment in CML patients. In the era of treatment-free remission as a primary endpoint, imatinib seems contraindicated in obese patients that need to reach early and deep molecular responses. Indeed, obesity seems an initial risk factor counterbalanced by the use of second generation TKIs, even if cardiovascular risk and other comorbidities should be taken into account in this subset of patients. Further validation of the prognostic value of BMI on large series of patients treated frontline with all available TKIs is needed to confirm its definitive role.

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Conflict of interest

All authors declare no conflict of interest.

Authors contribution

MB designed the study and analysed data and wrote the manuscript; MM collected data and wrote the manuscript; MC, GC and RL followed patients; DD performed molecular analysis; GA revised the paper; RF critically revised the paper and approved the final version.

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