ORIGINAL ARTICLE

Comparison of Clinicopathological Parameters, and Treatment Responses in Younger and Older Chronic Myeloid Leukaemia Patients Treated with Imatinib

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ABSTRACT

Introduction: Differences in baseline characteristics and response to treatment in different age groups of patients with chronic myeloid leukaemia (CML) in resource-limited countries have not been extensively studied. We aimed to determine the differences in clinicopathological parameters at diagnosis and response to imatinib in adult CML patients with younger (under 60 years; YCML) and older (60 years and older; OCML) age treated at our institution from March 2001 to March 2021. **Methods:** A retrospective analysis of consecutive adult CML patients receiving imatinib was performed. Clinicopathological parameters and treatment response were reviewed and analysed using hospital medical records and electronic data reports. **Results:** The median age at diagnosis was 50 years. OCML patients (n=17) had significantly more comorbidities. The YCML group (n=50) generally had a palpable spleen >5cm from the costal margin, mild anaemia, hyperleukocytosis and thrombocytosis. A starting dose of 400 mg/day was observed in 84% of YCML and in 65% of OCML. Cumulative complete cytogenetic response was 50% in YCML versus 70.6% in OCML, p=0.158. OCML tended to have a higher percentage of major molecular response (MMR) (52.9% versus 32%) and a shorter time to MMR, 22 months (range 5-70) versus 35 months (range 8-53). OCML experienced more haematological and non-haematological treatment-related adverse events after imatinib therapy. **Conclusion:** Although OCML patients had more comorbidities and treatment intolerances, overall long-term treatment response was comparable to YCML. In OCML, a more personalised approach to initial and subsequent dosing of imatinib may be considered.
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Keywords: Chronic myeloid leukaemia, Age, Imatinib, Response, Outcomes

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INTRODUCTION

Chronic myeloid leukaemia (CML) is a Philadelphia (Ph) chromosome myeloproliferative neoplasm (MPN) involving abnormal pluripotent stem cells. It develops as a result of reciprocal translocation of chromosomes 9 and 22, t (9;22), producing fusion BCR-ABL encodes a protein that causes dysregulation of tyrosine kinase activity (1). The discovery and subsequent introduction of tyrosine kinase inhibitor (TKI) in the treatment armamentarium of CML have transformed its management landscape (2). The International Randomised Study of Interferon and STI-571 (IRIS) trial showed that imatinib at a dose of 400mg once daily is more effective and associated with fewer side effects than interferon-alpha plus cytarabine in patients with newly diagnosed CML (2). The efficacy of imatinib persists over time, and its long-term administration was not associated with intolerable cumulative or late adverse effects (3).

CML occurs in all age groups, with the median age at diagnosis being around 55 to 65 years (4,5). The United Nations has defined the elderly as persons over 60 years of age (6), which is consistent with the Malaysian National Policy of Older Persons. In this study, we used the cut-off age of 60 and above to describe OCML for consistency, as these patients are most likely not eligible for allogeneic stem cell transplantation (SCT) in Malaysia and are not receiving SCT approaches to improve their prognosis

(7-9). Age-related physiological changes can affect drug tolerance and response to treatment. Studies have shown that older age is an unfavourable prognostic factor for patients with CML (10,11). In both pharmacological and allogeneic transplantation, older age has been shown to be associated with poorer treatment tolerability, poorer treatment response and poorer long-term survival (12). Despite increased toxicity, higher discontinuation rate and dose reduction in older patients, few studies have shown similar cytogenetics and molecular response to imatinib therapy in older and younger CML patients (13). However, the GIMEMA CML Working Party showed lower haematological and cytogenetic response rates in OCML, but similar progression-free survival (PFS) and overall survival (12). Cojbasic et al. showed significantly higher estimated 6-year event-free survival (EFS) in the middle-aged group (45 to 64 years) compared to young (18 to 44 years) and older patients (age ≥65 years) (10).

As our older-aged population is increasing, it is imperative to obtain information on treatment patterns, responses and outcomes, as different treatment strategies may need to be implemented depending on age and concomitant diseases, especially in countries with limited resources. Currently, there is limited data on differences in treatment patterns, response and outcomes from CML in the South East Asia region, particularly Malaysia. A study in India investigated the clinical characteristics, adverse effects and response to treatment in 712 CML patients, of whom 7.3% were older (≥ 60) (14). This study found that patient age does not affect the biology of CML and that TKI treatment can benefit older people as much as younger patients (14).

In this study, we aimed to determine the clinicopathological characteristics and treatment responses in adult consecutive CML patients receiving imatinib and determine the differences of these variables between age groups, younger-onset CML (YCML) and older-onset CML (OCML).

MATERIALS AND METHODS

Patients

We conducted a single-centre retrospective observational study at Hospital Canselor Tuanku Muhriz (HCTM, UKM). The study protocol was approved by the Medical Research Ethics Committee UKM (FF-2020-322) and followed the Declaration of Helsinki. Consecutive CML patients in the chronic phase diagnosed and treated in UKMMC were included in the study using convenient sampling. Our study included CML patients defined by the presence of Ph+ chromosome at diagnosis by conventional karyotyping, fluorescence in situ hybridisation (FISH), or real-time quantitative or qualitative polymerase chain reaction (PCR) guidelines. Patients who had a failure due to confirmed compliance issues were excluded from the study. The studied patients were divided into two age groups: younger-onset CML [YCML] (<60 years) and older-onset CML [OCML] (≥60 years).

Medical case notes were obtained from the Medical Record Office of HCTM, and electronic data records of all consecutive patients were reviewed. The recorded information included; i] socio-demographic data such as age, gender, ethnicity, comorbidity, and family history of malignancy; ii] CML disease characteristics such as symptoms at presentation, which included fatigue, weight loss, and abdominal fullness. Sokal (15) and European Treatment and Outcome Study (EUTOS) (16) scores, clinical and laboratory findings at presentation, and date of diagnosis; iii] imatinib treatment data such as date of initiation of imatinib, dose adjustment within the first year of imatinib therapy, any treatment-related side effects or adverse events (AEs), any changes to second-line TKI or non-TKI therapy such as interferon-alpha, chemotherapy or allogeneic hematopoietic stem cell transplant (HSCT) due to treatment intolerance or less favourable responses. The gradings of hematologic and nonhematologic treatment-related AEs were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5 (2017) (17). The adverse events during imatinib therapy were collected from documentation written in patients' medical records, and they were monitored in the clinic every one to three months.

Assessment of treatment response

The definitions of haematological, cytogenetic, and molecular responses were based on 2013 European LeukemiaNet (ELN) recommendations (18). A complete cytogenetic response (CCyR) is defined as no Ph+ metaphases detected, major molecular response (MMR) is defined by a ≥3-log reduction of BCR-ABL1 mRNA (or BCRABL1 ≤0.1%), and deep molecular response (DMR) is defined by a ≥4-log reduction of BCR-ABL1 mRNA (or BCR-ABL1 ≤0.01%). Cytogenetic testing was performed at our centre using standard banding techniques, with at least 20 metaphases analysed and FISH using dual probes for BCR and ABL1 genes, and if <20 metaphases were analysed, the cytogenetic test was performed using FISH using dual probes for BCR and ABL1 genes. Real-time quantitative PCR for BCR-ABL1 was conducted in the Molecular Diagnostic Laboratory, Department of Pathology, HCTM, till 2015, as described previously (19). It was subsequently performed in Sunway Medical Centre, Kuala Lumpur, from August 2016 onwards using the Xpert® BCR-ABL Ultra quantifies BCR-ABL1 mRNA level on the International Scale (IS) via calibration of the assay to the World Health Organization (WHO) international genetic reference panel for quantitation of BCR-ABL1 mRNA. The baseline was defined as 100% BCR-ABL1^{IS}, and MMR (3-log reduction relative to the standardised baseline) was defined as 0.1% BCR-ABL1^{IS}.

Imatinib intolerance occurs when patients cannot continue the first-line therapy due to side effects or

adverse events. Resistance to imatinib therapy is defined as one of the following: [i] failure to achieve complete hematologic response and BCR-ABL1 transcript levels less than or equal to 10% (IS) after 3 to 6 months of therapy or partial cytogenetic response by cytogenetics after 3 to 6 months of treatment; [ii] failure to achieve complete cytogenetic response or BCR-ABL1 transcripts (IS) less than or equal to 1% after one year or longer of therapy; or [iii] cytogenetic or hematologic relapse at any time beyond one year of treatment (secondary resistance to imatinib) (18). All patients were censored at the last contact or follow-up date. The follow-up period is the duration from the initiation of imatinib until 31st March 2021.

Statistical analysis

Data were entered into the Statistical Package for the Social Sciences (SPSS) version 25 software for further data cleaning and statistical analysis. Categorical variables were presented as frequencies and percentages. For quantitative variables, the normality of the data was assessed with the Kolmogorov-Smirnov test. Normally distributed quantitative data were expressed as mean ± standard deviation (SD), while those not normally distributed were expressed as the median and interquartile range (IQR) or range (minimum-maximum). The categorical data of clinical characteristics and treatment responses were compared between YCML and OCML groups by univariate analysis using χ^2 or Fisher's exact tests (if one or more of the variable values had an expected frequency of five or less). Mann-Whitney U tests were performed to compare quantitative data between YCML and OCML since the data was not normally distributed. All p-values were two-tailed, and values less than 0.05 were considered statistically significant.

RESULTS

From March 2001 to March 2021, 107 patients were diagnosed with CML at our centre. Their medical record files were searched from the Medical Record Department HCTM, but only 97 were available and screened for inclusion and exclusion criteria. Thirty patients had to be excluded from the study for various reasons (Fig. 1).

Baseline patients and disease characteristics

A total of 67 patients were included in this study. The baseline characteristics of these patients were stratified by age group, as summarised in table I. Patients were followed up for a median of 95 months. The median age of patients at diagnosis was 50 years (range: 18-75). Seventy-five per cent of patients were YCML. The majority of patients were male (n=47, 70.1%) and most were of Malay ethnicity (60.3%), followed by Chinese (25.4%) and Indian (4.5%). Thirty-one patients had comorbidities such as diabetes mellitus, hypertension, ischaemic heart disease, chronic kidney disease and stroke. This was significantly more common in OCML

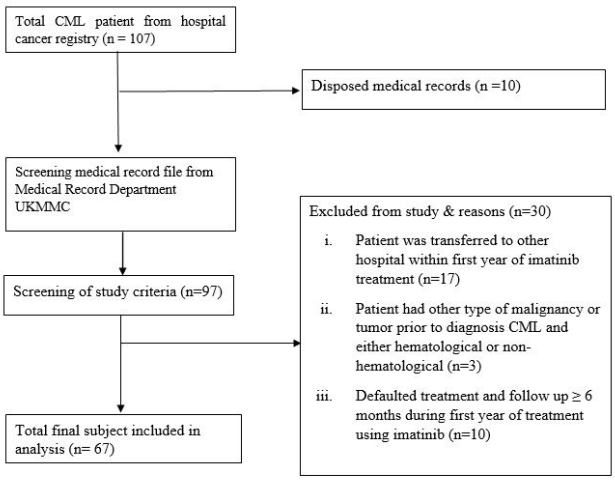

Figure 1: Flow chart showing subject recruitment into the study

patients than in YCML (88.2% vs. 32.0%).

Among all CML patients, 48 were symptomatic at presentation, with 63.9% of patients having splenomegaly of more than 5cm. However, six of 67 patients did not have documentation on spleen size at presentation. The presence of symptoms and splenomegaly >5cm at presentation were similar between both groups. Eleven (64.7%) of OCML and 37 (74.0%) of YCML were symptomatic at presentation. A higher percentage of YCML patients presented with splenomegaly >5cm at presentation. Most patients (66.7%) had hyperleukocytosis at presentation with median total white cell counts of 164.2 $x10^9$/L. YCML tended to have a higher white cell count level than OCML, with a median white cell count of 176 $x10^9$/L, p= 0.064, and YCML had a significantly higher rate of hyperleukocytosis as compared to OCML (75.5% vs 41.2%), respectively, p= 0.010. Both groups had thrombocytosis with platelet counts of 533$x10^9$/L in YCML and 513$x10^9$/L in OCML. Haemoglobin and platelet levels at presentation were statistically not significant in both groups.

Sixty-one out of 67 (91.0%) patients had Sokal and EUTOS scores at diagnosis. Six patients had no documentation on the measurement of spleen size at presentation. OCML patients had either intermediate or high Sokal scores (Table I). There was a higher percentage of YCML patients, 28 (63.6 %), with a high Sokal score compared to OCML patients, 9 (52.9%). Interestingly, more than 70.0% of patients had low EUTOS scores, and the distribution of EUTOS scores was similar in both age groups. There was no significant difference in the EUTOS score in both YCML and OCML groups, p>0.522.

Treatment pattern throughout the study

At presentation, 63 (94.0%) patients received pharmacological or non-pharmacological, non-TKI-based therapy, such as hydroxyurea, intravenous

Table I: Baseline demographics and disease characteristics of the CML cohort according to age groups

	All patients (n=67)	YCML (n=50)	OCML (n=17)	p-value
Age, median (range)	50 (18-75)	44 (18-59)	65 (61-75)	NA
Sex, n (%)				0.570[a]
Male	47 (70.1)	36 (72)	11 (64.7)	
Female	20 (29.9)	14 (28)	6 (35.3)	
Ethnicity, n (%)				#
Malay	41 (60.3)	29 (56.9)	12 (70.6)	
Chinese	17(25.4)	14(28)	3(17.6)	
Indian	3(4.5)	2(4)	1(5.9)	
Others	6(9)	5(10)	1(5.9)	
Any comorbidity, n (%)				**<0.001[a]**
Yes	31 (46.3)	16 (32)	15 (88.2)	
No	36 (53.7)	34 (68)	2 (11.8)	
Family history of malignancy, n (%)				0.103[b]
Yes	8 (11.9)	8(16)	0(0)	
No	59(88.1)	42(84)	17(100)	
Presence of symptoms				0.538[b]
Yes, n (%)	48 (71.6)	37 (74)	11 (64.7)	
No, n (%)	19 (28.4)	13 (26)	6 (35.3)	
Spleen size at diagnosis, n (%) [@]	n=61	n=44	n=17	0.088[a]
Not palpable and/or <5 cm from costal margin	22 (36.1)	13 (29.5)	9 (52.9)	
>5 cm from costal margin	39 (63.9)	31 (70.5)	8 (47.1)	
Blood counts at presentation				
Haemoglobin, g/dL	10.7 (8.8-11.9)	10.5 (8.8-11.8)	11.7 (8.8-13.7)	0.194[c]
White cell count, $x10^9$/L	164.2 (78.4-254)	176.0 (102.7-254)	78.4 (46.5-195)	0.064[c]
Platelet count, $x10^9$/L	519.5 (302-655)	533.0 (302-662)	513.0 405-573)	0.860[c]
Sokal score, n (%) [@]	n=61	n=44	n=17	#
Low	10 (16.4)	10 (22.7)	0(0)	
Intermediate	14 (23)	6 (13.6)	8 (47.1)	
High	37 (60.7)	28 (63.6)	9 (52.9)	
EUTOS score, n (%) [@]				0.522[b]
Low	48 (78.7)	35 (79.5)	13 (76.5)	
High	13 (21.3)	9 (20.5)	4 (23.5)	

Values are expressed in median (interquartile range) except age in median (range).
Symptoms including; fatigue, weight loss, abdominal fullness or/and splenomegaly.
[@]Sokal and EUTOS scores were available in 62 patients.
Abbreviations: EUTOS = European Treatment and Outcome Study, NA: not applicable
Statistical tests: a=Chi-Square test, c^2; b= Fisher Exact test; c=Mann-Whitney U test, were performed to obtain the p-value
p value was unable to be generated as the expected value <5 in each cell should not be more than 20% to perform chi-square test and not fulfil Fisher's exact test

cytarabine, busulfan, interferon-alpha, leukapheresis, which was administered either monotherapy or in combination (Table II). Four patients received front-line imatinib and did not require other therapies since they did not have hyperleukocytosis at presentation. Following the confirmation of CML diagnosis, the median duration from diagnosis to initiation of imatinib was 49 days and 40 days in the YCML and OCML groups respectively.

Among the OCML group, 11 (64.7%) started imatinib at the standard dose of 400 mg/day and 6 at the reduced doses: 2 at 100 mg/day, 1 at 200 mg/day and 3 at 300 mg/day, as they were deemed too frail for standard dose. During follow-up, 4 continued at 400 mg/day, 4 continued at <400 mg/day, and 4 required intermittent imatinib discontinuation due to various reasons, including intolerable side effects. Imatinib was permanently stopped in 5 patients and switched to nilotinib.

Among YCML group, 42 (84%) started imatinib at the standard daily dose of 400 mg. However, 8 patients were started with doses between 100 to 300 mg daily as they developed cytopenia from the initial cytoreductive agents prior to imatinib. The doses were subsequently increased to 400-600 mg/day. During follow up, 15 continued at 400 mg/day, 14 required intermittent imatinib discontinuation due to various reasons,

Table II: Treatment pattern among the CML patients

Treatment pattern	All patients (n=67)	YCML (n=50)	OCML (n=17)	p-value
Initial treatment				
Non TKI-based therapy	63 (94)	48 (96)	15 (88.2)	NA
Hydroxyurea only	35 (52.2)	26 (52.0)	9 (52.9)	
Hydroxyurea and cytarabine	14 (20.9)	12 (24.0)	3 (17.6)	
Hydroxyurea and busulfan	1 (1.5)	1 (2.0)	0 (0.0)	
Hydroxyurea and interferon alpha	6 (9.0)	6 (12)	0 (0.0)	
Leukapheresis alone	1 (1.5)	0 (0.0)	1 (5.9)	
Leukapheresis and cytarabine	1 (1.5)	0 (0.0)	1 (5.9)	
Leukapheresis with cytarabine and hydroxyurea	5 (7.5)	4 (8.0)	1 (5.9)	
TKI-based therapy (front-line imatinib)	4 (6)	2 (4.0)	2 (11.8)	
Duration from diagnosis to initiation of imatinib, day	47 (21.5-131)	49 (23-192)	40 (19-85)	0.476[c]
Blood counts at the time of initiation of imatinib				
Haemoglobin, g/dL	11.6 (6.7-15.6)	12.0 (6.7-15.6)	11.4 (7.0-14.5)	0.779
White cell count, $x10^9$/L	25.8 (4.0-432.0)	46.8 (4.0-309.1)	14.4 (5.3-432.0)	0.136
Platelet count, x 10^9/L	482 (100-1254)	465 (100-1254)	520 (213-1042)	0.937

Data presented as n (%). Values are expressed in median (interquartile range)
Abbreviation: TKI: tyrosine kinase inhibitor; NA: not applicable
Statistical tests: c=Mann-Whitney U test were performed to obtain the p-value

including intolerable side effects, and 2 discontinued permanently. Imatinib was permanently stopped in 18 patients, in which 15 were switched to nilotinib, 1 was enrolled in a clinical trial and 3 underwent allogeneic HSCT.

Prior to switching to second-line therapies, the patients were screened for BCR-ABL1 KD mutation. We found that 3 had T315I, 1 had L387F, 1 had V379I,and 1 had F359V mutations, all of which in the YCML. Meanwhile, 2 other patients had clonal cytogenetics evolution. The BCR-ABL1 KD mutational analysis was performed in Universiti Sains Malaysia utilising denaturing high-performance liquid chromatography and direct DNA sequencing method, and in HCTM using allele-specific oligonucleotide reverse transcriptase-polymerase chain reaction (RT-PCR) assay followed by direct sequencing technique. (20,21)

Cytogenetic and molecular responses

Responses to imatinib by age group are shown in Table III. Complete haematological response (CHR) to imatinib could not be accurately determined because patients received cytoreductive therapies prior to imatinib treatment, as shown in Table II. Based on the 2013 ELN guidelines treatment milestones, 5/50 (10%) YCML and 2/17 (11.8%) OCML achieved CCyR at 6 months, while 3/50 (6%) YCML and 2/17 (11.8%) achieved MMR at 12 months. After a median time of 64.4 (range 5.9-188.2) months from the start of imatinib treatment, 12 (70.6%) of OCML patients achieved CCyR, with 9 of them

Table III: Cytogenetic and molecular responses according to age groups

Response	All patients	YCML	OCML	p-value
Cytogenetic	(n=65)	(n=48)	(n =17)	
CCyR	36 (55.4%)	24 (50%)	12 (70.6%)	0.167[b]
Not in CCyR	29 (44.6%)	24 (50%)	5 (29.4%)	
Molecular	(n=67)	(n=50)	(n=17)	
MMR	25 (37.3%)	16 (32.0%)	9 (52.9%)	0.152[b]
Not in MMR	42 (63.7%)	34 (68.0%)	8 (47.1%)	
Duration of time from date of starting imatinib to				
Achievement of CCyR, month		16.9 (3.0-62.8)	12.8 (2.9-46.0)	0.33[c]
Achievement of MMR, month		35.0 (8.0-53.0)	21.9 (5.3-70.2)	0.157[c]

Values are expressed in median (interquartile range)
Abbreviations: CCyR=complete cytogenetic response; MMR=major molecular response
Statistical tests: c^2; b= Fisher Exact test; c=Mann-Whitney U test were performed to obtain the p-value
FISH analysis was not able to be performed in 2 cases due to insufficient cell counts

achieving MMR. Of these 12 patients, one developed a cytogenetic relapse and progressed to blastic phase. The other 11 remained in CCyR while receiving imatinib at the end of the study period. The 5 patients who did not achieve CCyR on imatinib were switched to nilotinib.

After a median time of 53.7 (range 5.6-201.3) months from the start of imatinib treatment, 24 (50%) of the YCML patients achieved CCyR, and 16 of them achieved MMR. Of the YCML patients in CCyR, 8 developed cytogenetic relapse. Eleven YCML patients developed a blastic phase (BP), including 4 who achieved CCyR but suffered a cytogenetic relapse. We thus found that the OCML group tended to have higher CCyR and MMR rates than the YCML group throughout the follow-up period. OCML also showed a trend towards a shorter time from starting treatment with imatinib to achieving CCyR and MMR compared to YCML, although this was not statistically significant.

Imatinib treatment-related adverse events

In the entire cohort of this study, 36 (52.9%) patients experienced one or more haematological and non-haematological adverse events (AE) following imatinib therapy (table IV). During the follow-up period, more treatment-related AE occurred in the OCML group than in the YCML group (70.6% versus 47.1%).

The commonest haematological adverse event following imatinib treatment was thrombocytopenia (69.4%), followed by leukopenia (66.6%) and anaemia (47.2%). OCML had a higher frequency of thrombocytopenia than YCML, 75% versus 66.7%. Both groups experienced similar percentages of anaemia and leukopenia. The most often non-haematological adverse event following imatinib treatment was gastrointestinal disturbance such as nausea, vomiting, bloating and diarrhoea, accounting for about 50% of patients that experience these adverse events during imatinib treatment. The symptoms were present in 58.3% of OCML and 45.8% of YCML.

Table IV: Summary of treatment-related adverse events reported during imatinib therapy according to CTCAE version 5 (2017)

	All patients (n=67)	YCML (n=50)	OCML (n=17)
Any Grade	36 (52.9)	24 (47.1)	12 (70.6)
Haematological			
Anaemia	17 (47.2)	12 (50.0)	5 (41.7)
Platelet count decreased	25 (69.4)	16 (66.7)	9 (75.0)
White blood cells decreased	24 (66.6)	16 (66.7)	8 (66.7)
Non-haematological			
Nausea, vomiting, bloating and diarrhoea	18 (50.0)	11 (45.8)	7 (58.3)
Alanine aminotransferase and blood bilirubin increased	14 (38.9)	12 (50.0)	2 (16.7)
Muscle cramp, myalgia and pain in extremity	13 (36.1)	13 (54.2)	0 (0.0)
Pruritus and urticaria	6 (16.7)	4 (16.7)	2 (16.7)
Bacteraemia, viremia and fungemia	5 (13.9)	4 (16.7)	1 (8.3)
Generalized edema and limbs oedema	4 (11.1)	3 (12.5)	1 (8.3)
Palpitation and ventricular arrhythmia	1 (2.8)	1 (4.2)	0 (0.0)
Others	8 (22.2)	7 (29.2)	1 (8.3)

Data presented as n (%)
*One patient may have more than one side effect. Others included fatigue, malaise, headache, hyperglycemia, and watery eyes

DISCUSSION

This study highlights the latest data on CML in our cohort of multi-ethnic populations in a single tertiary centre in Klang Valley, Malaysia, and the differences in baseline characteristics and response to treatment between YCML and OCML. In this study, the mean age of our cohort at diagnosis was 50 years. This result was comparable to previous studies conducted locally and in other Asian countries that found a mean age between 40 and 50 years (22-26). Data from Western countries, including epidemiological registries, showed the mean age at diagnosis was between 55 and 60 years (4,27,28). In terms of ethnicity, the highest proportion of CML patients in our study were Malays, followed by Chinese, Indians and others. The ethnic distribution of patients in this study was representative of the current Malaysian population, which is composed of Malays (69.8%), Chinese (22.4%), Indians (6.8%) and others (1.0%) (29).

We found that the YCML group had a palpable spleen > 5 cm from the left costal margin, mild anaemia, hyperleukocytosis and thrombocytosis compared to the OCML group. As OCML was significantly associated with comorbidities in our cohort, this group may have been routinely clinically assessed and monitored for underlying disease. We believe this may explain why CML was detected at an earlier stage of disease in OCML and thus had lower disease activity, reflected in a lower proportion of patients with anaemia, hyperleukocytosis and thrombocytosis. Cojbasic et al. also observed that the young group (18-44 years) had mild anaemia with a median Hb of 10.4g/dL (10). All patients in their cohort had hyperleukocytosis regardless of age (10). Interestingly, our YCML group had hyperleukocytosis more frequently. Splenomegaly is attributed to extramedullary haemopoiesis. In the presence of thrombocytosis, this could also be due to an accompanying immune-inflammatory reaction, which is more likely to occur in the more immunocompetent YCML than in OCML (30).

The disease's nature at the time of presentation is an important factor in treatment response and outcome (30). The more advanced phase of CML typically had a poor response to treatment due to resistance to therapy and a poorer prognosis with complications from infection and bleeding (31,32). In the present study, all OCML patients had intermediate and high Sokal scores compared to YCML. Only a few studies reported similar results (10,30). However, in our study, no significant difference in EUTOS scores was found between YCML and OCML. Interestingly, more than 70% of patients in both groups had low EUTOS scores. Since the number of patients in our study was smaller, especially in the OCML group, and the data on spleen size at diagnosis was incomplete, this may not be a true result. However, Chhikara et al. also reported that 64.6% of their patients had medium and high Sokal scores, but using the EUTOS score, 81% had low scores (33). This could be due to the different variables that make up the other risk scoring systems.

Most of our cohort of newly diagnosed CML at our centre received non-TKI-based therapies at presentation. This was mainly for urgent cytoreduction. Only four patients were able to receive upfront imatinib as their first line of treatment, as imatinib was readily available to these patients via self-pay or through their employer and no urgent cytoreduction was required. The median duration of initiation of imatinib treatment from diagnosis was 47 days, and there was no statistically significant difference between YCML and OCML. Novel targeted therapies, which are often expensive, are not fully subsidised in Malaysia. Imatinib was first made available under the (Gleevec® International Patient Assistance Programme) GIPAP around 2002 and then included in the HCTM hospital formularies from January 2009. Funding issues are always at the forefront when choosing the best treatment option for CML worldwide, including Malaysia (23,25). This issue could therefore explain why most of our patients could not be treated with imatinib immediately after diagnosis and that there was a period of 2-3 months before funding or sponsorship was actually approved at the present time.

Age-related physiological changes have been shown to influence patients' tolerance to medical treatment. Therefore, patients' preferences and quality of life should be considered when weighing risks and benefits during the initial medical assessment. Although our study showed that OCML were more likely to experience dose reduction and treatment discontinuation than YCML, this was not significant. This was not surprising as there was a significantly higher percentage of imatinib intolerance

and adverse events of any grade in this age group (tables II and IV). Few studies have shown that the percentage of patients permanently stopping or reducing the dose of imatinib is significantly higher in older patients (12,34). Data from the SIMPLICITY study showed that intolerance to TKIs increased more in the first year of treatment. Therefore, intolerance and resistance to TKIs were the trigger for treatment modifications and changes in routine clinical practise (35). It is noteworthy that in our study, more YCML patients discontinued imatinib or were switched to nilotinib. Given the limited access and even lower allocation of nilotinib as second-line therapy in our centre, nilotinib was prioritised in YCML patients with imatinib intolerance or resistance.

In general, we followed the 2013 ELN guidelines regarding the timing of response assessment and treatment milestones. However, most of our patients were unable to adhere to the schedule due to financial constraints, inability to pay the fees for the assessment, logistical constraints and working time constraints. Therefore, the timing of the screening might have influenced the time to response in our patients. Nevertheless, our study showed an improvement in cumulative MMR rates with imatinib compared with previous local studies (26,36). Patient-supported programmes, better access to imatinib and regular patient education programmes may have contributed to this result. Cumulative CHR and CCyR were similar in both age groups. Consistent with our results, some authors reported similar CCyR (75-85%) between younger and older age groups (10,34). In contrast, studies by Rosti et al. and Cortes et al. found that older patients had significantly lower CCyR percentages (36-45%) (7,12).

Nevertheless, in our study, the OCML group tended to have a higher MMR rate and a shorter time to MMR compared to the YCML group, despite the change in treatment, although this result was not statistically significant. This could be due to an improvement in the tolerability of imatinib after the lower initial dose and/or treatment changes after the first year due to side effects. The GIMEMA CML research group found in their study of 2784 patients that the rates of CCyR and MMR were significantly lower in younger age groups (30). On the other hand, Cojbasic et al. found that the significantly higher MMR was most significant in the middle age group (10). Gugliotta et al. found no difference in MMR rates at 6, 12 and 18 months or in the cumulative incidence of MMR (87.4% or 89.7%) (37). The inconsistencies in the results are multifactorial. YCML in our cohort tended to have a higher burden of disease at presentation and sought medical attention later than OCML. The higher burden of disease, which took the form of splenomegaly, hyperleukocytosis, a higher degree of thrombocytosis and mild anaemia, was most common in the adolescent and young adult (AYA) group compared with adults (30-59 years), and the lowest rate was observed in older patients (≥60 years) (38). Cortes et al. found that splenomegaly had a higher rate in patients < 60 years (7). Six YCML patients had BCR-ABL1 KD mutations, including three with the T315I mutation, while two developed clonal cytogenetic evolution, which resulted in poor response to treatment as reported in previous studies (39,40). There was also a higher percentage of YCML patients exposed to cytotoxic agents at the presentation of CML prior to initiation of imatinib treatment, which may predispose the patients in this study to cytogenetic and molecular aberrations. Studies have shown that previous cytotoxic therapies have a significant impact on cytogenetic development, especially when previously treated with intensive chemotherapy, busulphan and interferon and least with hydroxyurea (41).

Another aspect to consider is poor treatment adherence. Treatment adherence has a significant impact on treatment response and outcomes in CML (42). Haque et al. found that patients with higher TKI adherence had lower rates of progression to accelerated phase/bladder crisis and mortality than patients with lower adherence (43). Younger patients were found to have lower adherence (41,42,44,45), which could be due to factors such as work or study commitments. In contrast, Noens et al. found in the ADAGIO study that older age was a factor that negatively influenced adherence, and that this negative effect did not significantly influence adherence (45,46). Another important approach to ensuring adherence is routine or frequent PCR monitoring, which has been shown to significantly reduce the risk of progression or mortality, benefiting both high and low TKI adherence groups (43).

Besides assessing the treatment pattern, modification, and response, safety and treatment-related adverse events are also important factors in treating CML patients. This study found that OCML had higher haematological and non-haematological treatment-related AEs following imatinib therapy. Notably, 70.6% of OCML and 47.1% of YCML were reported to have experienced both treatment-related AEs. Previous studies have reported that the whole cohort of their research was mild or moderate in intensity and resolved spontaneously or with dose interruptions or reductions, as needed (10). The elderly patients of their cohort experienced more treatment-related side effects, both haematologic (young patient; 26.7%, middle-age patient;15.8% and elderly age; 19.8%), and non-haematologic (40.0%), as compared with the young (18.1%) and middle-age patients (15.8%) (10). We found that the commonest non-haematological AEs following imatinib was a gastrointestinal disturbance. Our study showed OCML had prone to develop these adverse events. However, we could not report the severity of the AEs due to incomplete records. Previous studies found that older patients had experienced significantly higher rates of non-haematological AEs following imatinib, such as oedema, nausea, skin reaction and cardiopulmonary

toxicity (10,34).

The most common haematological adverse event in our study after treatment with imatinib was new-onset thrombocytopenia and neutropenia (69.4% and 66.6%, respectively). This treatment-related event has also been reported in previous studies in Asian and Western patients (25,47). In our study, YCML patients tended to have lower haemoglobin levels at diagnosis, and the rate of anaemia at diagnosis did not differ in the two groups (YCML;42.9% and OCML;47.1%). After imatinib therapy, both groups also showed similarities in the development of new-onset anaemia or reduction in haemoglobin levels during imatinib therapy, with a higher rate in YCML (50% versus 41.7%). A study conducted in Brazil came to a similar conclusion: patients aged < 60 years had a higher tendency to develop anaemia after two years of imatinib treatment (64% vs. 36%). However, this was not statistically significant (48).

There are some limitations to this study. First, the data were collected retrospectively and, as with other longitudinal studies, missing data are inevitable. In addition, some inactive medical records were disposed of during the study period. Secondly, other possible factors affecting treatment response and outcome, such as compliance and adherence to imatinib treatment, financial aspects and drug-drug interactions, need to be further investigated and assessed. Finally, the samples were selected on the basis of random sampling, i.e. there was no proper randomisation, so this is prone to selection bias and may not be representative of the general population of CML. As the number of OCML patients in our cohort was small, a multicentre, longitudinal study design should be considered to determine the most appropriate dose to help OCML achieve CML treatment milestones with routine assessment of adherence.

CONCLUSION

In summary, we found that YMCL tended to have a higher disease burden at diagnosis and resistance to imatinib, while OCML had significant comorbidities and treatment intolerance. Both the YCML and OCML groups achieved treatment milestones at CML at comparable percentages, albeit over a longer period of time.

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