Comorbidities and polypharmacy impact on complete cytogenetic response in chronic myeloid leukaemia elderly patients

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A B S T R A C T

Background: In older patients comorbidity and polypharmacy can significantly influence the success of the treatment, as well as the cognitive and psycho-social aspects. A significant proportion of chronic myeloid leukaemia (CML) patients are “elderly”; in the past the aim of therapy in this subset of patients was only to contain the leukaemic mass, but nowadays, with the advent of the protein-tyrosine kinase inhibitors, also elderly patients can access these treatments. We want to assess if even old CML patients, with a correct geriatric evaluation, can be successfully treated with protein-tyrosine kinase inhibitors.

Methods: A complete geriatric evaluation in 16 old CML patients aged >65 years treated with TKI was performed in order to assess the comorbidity, the polypharmacy and the cognitive, physical and psychological states. The Charlson comorbidity index (CCI) and the polypharmacy were correlated to the obtained cytogenetic response. Seven scales of geriatric evaluation were used to assess the autonomy of patients before they were included into the study.

Results: In our cohort of elderly patients treated with imatinib, comorbidities and polypharmacotherapy demonstrated an influence on TKI therapeutic success. In fact, the majority of complete cytogenetic response was obtained by patients who presented a low score of CCI and did not take any other drugs other than TKI.

Conclusion: Also old chronic myeloid leukaemia patients can benefit from TKI treatment if a good cooperation between the haematologist and the geriatrician is established.

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1. Introduction

More and more elderly people with cancer are being treated in oncology clinics worldwide every year, many of whom have co-morbid disorders treated with one or more drugs resulting in adverse effects associated with polypharmacy and drug–drug interactions. This is due to patients’ altered pharmacokinetic/pharmacodynamic state which reduces the therapeutic window associated to anti-neoplastic agents. Therefore, in older patients comorbidity and polypharmacy can significantly influence the success of the treatment, as well as the cognitive and psycho-social aspects [1,2]. In patients with BCR-ABL1 positive chronic myeloid leukaemia (CML) age represents a consistently poor prognostic factor too and has become a variable of considerable importance in the main prognostic indices e.g. Sokal, Euro [3,4]. Unfortunately a significant proportion of CML patients are in fact “elderly” according to the most widely accepted definition of “old person” (age > 65 years). CML is the first onco-haematological disease with a well recognised karyotypic hallmark. Ten years ago the aim of the therapy in this subset of patients was only to contain the leukaemic mass due to the fact that older patients did not have access to appropriate treatments like interferon or allogenic bone marrow transplantation [5]. Nowadays with the advent of the protein-tyrosine kinase inhibitors (both first and second generation), the aim of the therapy is more ambitious because these drugs are a targeted treatment. TKIs are delivered orally with minimal side effects and able to achieve a complete response also in this subset of patients minimising significantly poor prognostic impact of age [6–8]. Even if elderly patients are treated with imatinib, they are not enrolled in clinical trials [9]. As it might be expected, older patients experience more adverse effects, both haematologic and non-haematologic, but they are clinically heterogeneous. Above all adverse events of TKIs are associated with lower adherence; this aspect is very important because it prevents a long term positive outcome in older as well as in younger patients [10,11]. There are only limited data in literature on the role of comorbidities in CML older patients [12]. The aim of this study was to retrospectively evaluate the impact of comorbidities and...
polypharmacy, to obtain complete cytogenetic response at six months in a group of elderly CML patients treated with imatinib.

2. Methods

CML outpatients consecutively observed from 2006 to 2011 in our Institution were totally 103 and they were all treated with TKI. However only 16 of them were at least 65 years old when CML diagnosis was made.

They were stratified at diagnosis according to Sokal score risk and treated with imatinib. When they were enrolled in this study, instruments to assess patient-related factors recommended for a comprehensive geriatric assessment were used. Charlson comorbidity index [13] represents the most commonly used score in oncology to classify comorbidity with a simple, readily applicable and a valid method to estimate risk of death from comorbid disease and mood and cognitive status predictors including abnormal cognition defined as Mini Mental State Examination (MMSE) score < 24 [14]. Functional status predictors including poor physical performance defined by two measures of disability: difficulty with any of the basic activities of daily living (ADL) e.g. bathing, dressing, toileting, moving around, continence and feeding [15]; difficulty with any of the following four non gender-dependent, instrumental activities of daily living (IADL) e.g. the use of the telephone, taking medicine, travelling and managing money [16]. The total score ranges from 0 to 6 (ADL) and from 0 to 8 (IADL). Scores less than maximum in ADL and IADL denote dependency. The Vulnerable Elders Survey (VES-13) is a simple function-based tool for screening community-dwelling populations to identify older persons at risk for health deterioration [17]. The VES considers age, self-rated health, limitations in physical function, and functional disabilities. The frailty status of the participants was evaluated according to recent SOF criteria [18], which are regarded to be just as effective as the frailty criteria of Fried et al. [19,20] in predicting adverse health outcomes, however they are easier to apply. The SOF index is composed of three items: 1) intentional or unintentional weight loss > 5% in the past year; 2) inability to rise from a chair five consecutive times without using the arms, and 3) self-perceived reduced energy level as described by a negative answer to the question “do you feel full of energy?” Subjects are considered “frail” if at least two of the three criteria are fulfilled, “pre-frail” if only one criterion is present and “robust” if none of the criteria is present. The Mini Nutritional Assessment (MNA) [21], evaluates dietary intake, anthropometrics, self perceiving nutrition and health and is an effective indicator of nutritional status (8–10 = at risk of malnutrition, ≤ 7 = malnutrition). The Geriatric Depression Scale (GDS) [22] is a self-reporting questionnaire designed specifically to screen for depression in older adults. A score higher than 5 suggests depression. Furthermore, this multidimensional geriatric assessment evaluates the independence of the patients before inserting them into the study. Polypharmacy was assessed reviewing patient medical records in order to find out the number and type of medications taken concomitantly with TKI. For each medication, research of its potential interaction with the TKI was performed.

The Charlson index and the polypharmacy were retrospectively correlated to the cytogenetic response and the necessity to change therapy. Statistical analyses were performed using MedCalc software [23]. All investigations were approved by the local ethics committee and all patients gave their informed consent.

3. Results

There were 9 males and 7 females with a median age of 72.7 (range 65–88). According to Sokal Score, 4 patients were classified as low risk (LR), 7 patients as intermediate risk (IR) and the remaining 5 as high risk (HR). All low risk patients achieved CCyR at 6 months, as well as three of the seven patients with intermediate risk and two of the five high risk patients. The correlation between Sokal score and CCyR was statistically significant. In two out of seven IR patients and in three out of five HR patients it was necessary to switch to second line TKI, two for CCyR loss, two for imatinib resistance and the last one for disease progression to blastic phase. Among second generation TKIs, four patients received dasatinib and one nilotinib. We also performed a correct geriatric evaluation in order to assess the comorbidity, the polypharmacy and the cognitive, physical and psychological states.

The Charlson comorbidity index was 0 in five patients, 1 in seven patients, 2 in only one patient and 3 or more in the three remaining patients. Among the five patients with CCI = 0, four of them achieved CCyR, the same for four out of seven patients with CCI = 1, only one patient with CCI = 2 and none of the three patients with CCI ≥ 3. Among the patients who switched to second line TKIs, two had a CCI of 1, one had a CCI of 2 and the other had CCI of 3 or more. Regarding polypharmacy four patients didn’t take any other drugs, five patients were taking one or two concomitant drugs and the other seven were taking three or more drugs. CCyR at 6 months was obtained by three of the four patients who didn’t take any other drugs except TKI, two out of five patients who took one or two other drugs and four out of the seven patients in therapy with three or more concomitant drugs (Table 1). Among patients who were in therapy with other drugs other than TKI, a correlation with the need for dose reduction was observed. The MMSE test showed that all the patients enrolled were cognitively intact, in fact all of them reached scores higher than 25 points, which is traditionally considered normal: of the sixteen patients five reached scores of 30, four obtained scores of 29, four scores of 28 and three scores of 27 (Table 2). Also scales of functional dependence showed optimal autonomy in the patients, in fact all of them reached the maximum score. Almost all the patients assessed by VES-13 and SOF evidenced a lack of vulnerability and fragility: analysing the VES-13 scores ten patients reached 0 score, four patients obtained 1, one scored 3 and one scored 6; on the other hand the scores obtained in the SOF test showed twelve nonfragile patients and only four prefragile patients. Moreover the scores of MNA confirmed an optimal nutritional state considering that all the scores were higher than 24 points: two patients reached a score of 30, four got a score of 29.5, four attained 29 points and five reached 28.5. Finally, mood analysis assessed by GDS showed very good scores: fourteen patients reached the maximum and only one patient scored 1.

4. Discussion

Comorbidities were identified as significant determinants of response to therapy in elderly patients with acute myeloid leukaemia,
breast cancer, head, neck and lung cancer, but an older age was consid-
ered a bad prognostic factor also in patients affected by CML [24]. Age is
then incorporated in the most important and worldwide used risk-score
assessments: Sokal score, referring to patients treated with convention-
al chemotherapy (1984), and EURO score, for patients treated with inter-
feron (1998) [3,4]. Then, before the advent of tyrosine kinase inhibi-
tors, physicians preferred to avoid such therapies. CML management
has dramatically improved after the introduction of imatinib in the begin-
ing and dasatinib and nilotinib some years later [25]. Phase I and II studies established the safety of imatinib and demonstrated its ability
to induce a high haematologic and cytogenetic response rate in CML pa-
tients. The follow-up analysis of IRIS study showed that the outcome at
8 years was according to cytogenetic response at different time points
[26–28]. Currently, the most powerful surrogate endpoints of long
term outcome is complete cytogenetic response (CCyR) at 12 months
as defined by 2009 European LeukemiaNet [29] and more recently the
update of recommendations defined optimal response at 6 months
[30]. Imatinib is a clear example of ideal drug treatment for a disease
such as CML: it is given orally, the incidence of relevant, severe toxicity
is relatively low, a proper dose management allows long term treatment
and responses in most of patients. It seems to have reduced the prog-
nostic role of age and some studies reported similar results in both
younger and elderly patients [5,6,31]. These data are confirmed also in
second generation TKIs treated patients [7,8]. In order to prevent the
risk of treatment failure it is necessary to assess the comorbidity factors,
the polypharmacy, and the cognitive and psycho-social state which is ab-
olutely essential for the adherence to the therapy because the patients
are treated at home [2,11,32]. Charlson Comorbidity Index is a list of co-
morbidities with a weight assigned from 1 to 6 derived from relative
risk estimates of a proportional hazard regression model using clinical
data [13]. Moreover interactions between TKIs and drugs used to treat
comorbidities can occur. Such drugs are extensively metabolised by
CYP450, whose activity is characterised by a considerable inter-
individual variability. CYP450 activity may be altered by several drugs:
some of them, when administered concomitantly, inhibit its activity in-
creasing TKI concentration, while others are inducers resulting in a de-
crease of TKI exposure. This may augment or lower patient exposure
to the drug, thus potentially leading, respectively, to undesired toxic ef-
effects or lack of therapy efficacy. Analysing a list of concomitant drugs
taken by patients for chronic illnesses, a considerable number of agents
interacting with TKIs were found, with the most frequent being ACE in-
hibitors, beta blockers and benzodiazepines. Physicians should be aware
of this eventuality in order to choose the best available therapeutic op-
tion to minimise risk of interactions [12,23,34]. In our CML patients pre-
viously treated with more than 3 drugs that interact with TKI metabolism, it was necessary to reduce TKI daily dose, as polypharamco-therapy influenced TKI therapeutic success.
In the majority of patients who obtained CCyR, they scored low on
the CGI and did not take any other drugs other than TKI.
Co-morbidity and polypharmacy also resulted in the need for change
therapy, in fact not one of the patients with CGI = 0 and noncomorbidant therapy needed to change TKI. In the case of co-
morbidities, TKIs are often administered at a lower dosage and this
may be associated to the lack of drug efficacy and consequently to the
need for change therapy, which was observed in some of our patients.
Another reason for the administration of lower dosage is the prevention
of adverse drug reactions, where risk augments with the number of co-
morbidities and of concomitant drugs taken by the patient. A reduced
concentration may cause a loss or resistance to the drug, thus making a
TKI change necessary; on the other hand, also an augmented concen-
tration of TKI or concomitant drugs may be equally risky and lead to the
need of changing therapy. In the resistant patients, second generation
TKIs were used (in four dasatinib and one nilotinib). Few data were
reported for elderly patients treated with dasatinib and nilotinib after
resistance or intolerance to imatinib [35,36]. Also in our cases no par-
cular difference was revealed in terms of haematological side effects if
the choice of second TKI takes into account co-morbidities and concom-
itant drugs [37].

5. Conclusion

In the era of target therapies in haematology and oncology, it would
be reasonable to define old patients on the basis of partially or completely
age-independent indicators of fragility rather than simply according to
years of age. We know that our sample is limited but there is very little
data to be found in literature, but our results suggest that also old
chronic myelogenous leukaemia patients can benefit from TKI treat-
ment, if a multidisciplinary approach is established between the
haematologist and the geriatrician. The assessment of co-morbidities
and polypharmacy state, including cognitive and psycho-social states,
for each patient before starting TKI therapy is absolutely essential to
predict compliance of patient to the therapy and the chances of thera-
petic success. We believe that the assessment of these parameters
should enter in clinical management.

Conflict of interests

All authors declare that they have no any actual or potential conflict
of interest including any financial, personal or other relationships with
other people or organisations within three years of beginning the sub-
mitted work that could inappropriately influence, or be perceived to in-
fluence, their work.

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