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Reconstructing CML guidelines for first line treatment from two different points of view

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TO THE EDITOR:

The treatment of Chronic Myeloid Leukemia (CML) with imatinib is a hallmark of targeted therapy, with life expectancy of CML patients now similar to that of the general population [1–4].

Imatinib is also a safe drug, with a benign safety profile [5].

Second and third generation TKIs (2GEN) were moved to first line indication due to faster cytogenetic and molecular responses [6].

However, randomized clinical trials have failed to show significant differences in overall survival (OS) or in protection from progression to accelerated phase (AP)/ blast crisis (BC) between imatinib and 2GEN, which also show less favorable safety profiles [5].

Despite these findings, several CML treatment guidelines recommend 2GEN over imatinib or in alternative to it in many subgroups of CML patients [7, 8].

The GIMEMA guidelines [7], Fig. 1A), were used as reference. The analysis was restricted to patients up to 80 years.

Six physicians who just completed their Medical School training and entered the Post Graduate School of Hematology at the University of Milano Bicocca took part in this experiment.

They were randomly divided into two groups.

Group 1 ("physicians") included three participants. They were instructed to review all scientific literature on first line treatment of CML and to provide treatment recommendations based on clinical trials results with emphasis on controlled studies.

Group 2 ("pharma executives") received the same literature but were asked to identify data that could maximize the 2GEN market share, avoiding openly illogical or illegal choices.

Results are expressed as mean ±95% confidence interval (95% C.I.) and comparisons were performed by 2 tail Student t-test.

The physicians' group concluded that among more than 15 controlled studies there was no convincing difference between imatinib and 2GEN in OS or PFS values. The safety data favored imatinib over 2GEN. Therefore, the decision was to consider imatinib as the drug of choice in all subgroups (Fig. 1B).

The introduction of 2GEN nevertheless leads to an important therapeutic dilemma for the doctor when starting treatment, also considering the different age groups.

For patients older than 40 years increased age-related comorbidities, especially metabolic and cardiovascular, made 2GEN choice not acceptable. Therefore, imatinib was preferred based on its efficacy and reduced toxicity.

In young patients the choice of therapy must necessarily take into account the factors related to the patient's young age and long life expectancy. Low SOKAL score: in these patients imatinib was favored for its excellent efficacy and minimal side effects, preserving 2GEN options for subsequent lines of therapy, if needed.

Intermediate/High SOKAL: the faster cytogenetic and molecular remissions related to the use of 2GEN are enticing but the data do not justify the use of these drugs. In fact, the use of 2GEN would not entail a clinical advantage for the patient but simply a faster improvement of laboratory tests without significant differences in PFS data, in exchange for an increase in cardiovascular and other serious AEs. Even in young women desiring pregnancy, imatinib was considered acceptable, as treatment could be safely paused during early gestation and resumed in the second/third trimester without substantial maternal or fetal risks [9].

Interestingly, the group initially considered 2GEN for young patients with high Sokal score. When this specific category was discussed, the proponents admitted that their choice was not based on evidence but on their own fear for the outcome of the patient.

The pharma executives' group focused on highlighting data that could support the use of 2GENs as a first line option. While acknowledging the lack of OS or PFS superiority, they emphasized the "sooner and faster" molecular responses seen with 2GENs in controlled trials. They argued that this could potentially translate into higher rates of treatment-free remission, although such an outcome remains unproven. Based on this rationale, they recommended 2GENs for nearly all subgroups, with the exception of older patients with low Sokal risk, where toxicity greatly outweighed potential benefits. Their choices are presented in Fig. 1C.

Some further considerations emanating from this group discussion are presented here below.

Young patients (<40 years) are eligible for 2GEN regardless of Sokal score. In this category of patients, the risk of cardiovascular events is low.

A similar reasoning was applied to patients aged between 41 and 65 years with a low ASCVD risk category: the first choice would be 2GEN.

The most controversial category is the over-65s with a high or intermediate Sokal score: the pharmaceutical company executives exploited the clinicians' fears of an aggressive disease to advise the prescription of 2GEN, willing to 'take the risk' of an adverse event in order to obtain a rapid induction of MMR in this category that epidemiologically comprises a high number of patients affected by CML.

The two groups of doctors produced dramatically different guidelines: the "physicians group" indicated imatinib as initial treatment for all groups, while the "pharma executives" suggested 2GEN TKIs for all but one category (Fig. 1D).

When compared with GIMEMA guidelines the physicians' recommendations diverged completely in 5 out of 9 categories (55%, 95% C.I. 26–81%) and partially (imatinib vs. 2GEN or imatinib) in 8 of 9 categories (88.9%, 95% C.I. 60–99%). Agreement occurred in only 1 category (11.1%, 95% C.I. 7–39%). Conversely,

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SOKAL	AGE<40	AGE 41-65	AGE 65-80
LOW	2GEN	IMATINIB-2GEN	IMATINIB
INTERMEDIATE	2GEN	2GEN	IMATINIB-2GEN
HIGH	2GEN	2GEN	IMATINIB-2GEN

A

SOKAL	AGE<40	AGE 41-65	AGE 65-80
LOW	IMATINIB	IMATINIB	IMATINIB
INTERMEDIATE	IMATINIB	IMATINIB	IMATINIB
HIGH	IMATINIB	IMATINIB	IMATINIB

B

SOKAL	AGE<40	AGE 41-65	AGE 65-80
LOW	2GEN	2GEN	IMATINIB
INTERMEDIATE	2GEN	2GEN	2GEN
HIGH	2GEN	2GEN	2GEN

C

SOKAL	AGE<40	AGE 41-65	AGE > 65
LOW	Imatinib – 2GEN	Imatinib – 2GEN	Imatinib – Imatinib
INTERMEDIATE	Imatinib – 2GEN	Imatinib – 2GEN	Imatinib – 2GEN
HIGH	Imatinib – 2GEN	Imatinib – 2GEN	Imatinib – 2GEN

Physicians — Same drug proposed

Pharma executives — Different drug proposed

D

Fig. 1 First line CML treatment recommendations according to different perspectives. A GIMEMA guidelines [7]. **B** Physicians' perspective. **C** Pharmaceutical company's perspective. **D** Physicians' and pharmaceutical company's choices compared. Green: concordance. Violet: discordance.

the pharma executives' guidelines showed no total disagreement (0%, 95% C.I. 0–25%) and only partial disagreement in 3 out of 9 categories (33%, 95% C.I. 11–63%), aligning completely with GIMEMA in 6 categories (66.7%, 95% C.I. 37–89%). Notably, the difference in full disagreement with GIMEMA guidelines between the two groups (physicians 55% vs. pharma executives 0%) reached statistical significance ($p = 0.04$).

This exercise involved young physicians entering their career path in Hematology, who had not yet been exposed to influence from pharmaceutical companies. They were asked to formulate first-line treatment guidelines for CML from two different perspectives. The results show a striking alignment between guidelines enacted by a cooperative group (GIMEMA in this case) and the recommendations generated by the group adopting a pharmaceutical industry perspective, rather than those based strictly on clinical trials evidence.

Similar considerations could be done for other guidelines, such as NCCN guidelines.

Guidelines should synthesize evidence emanating from clinical studies, especially from controlled clinical studies. In real terms they often represent the consensus of experts that are not immune from pressure from industry. Industry influence can occur both overtly, through incentives or professional advancements, and subtly, via the selective inclusion in educational and scientific events of physicians who are in line with company strategies and the exclusion of those who are not. This is particularly worrying,

given that many non-specialist clinicians rely on these guidelines without the tools to critically assess the underlying evidence. The decision tree adopted in the paper describing the generation of the GIMEMA guidelines [7] is a proof in this respect.

It is essential that guidelines be developed by independent experts with a focus on patient benefit. Otherwise, the risk is that guidelines will lose their function, becoming marketing tools.

It is encouraging that when prescription patterns are studied, they seem not in line with these guidelines [10, 11]. A recent study of CML prevalence in Lombardy showed that in 2022, over 75% of first-line treatments still involved imatinib [12], possibly reflecting clinician experience and cost-effectiveness considerations.

At the end of this work, we want to summarize the two different points of view that guided the whole task. Indeed, the two groups have considered different aspects as priorities for the treatment of CML. Comparing all recommendations the physicians' group diverged totally or partially from GIMEMA in 8 out of 9 patient categories. The group adopting an industry-oriented viewpoint differed, and only partially, in 3. The physicians' group totally disagreed with the GIMEMA recommendations in 5 out of 9 cases while the group guided by industrial interests differed totally from the GIMEMA recommendations in 0/9 cases.

This fact points again to the extent to which guideline content may reflect commercial priorities. Both groups gave priority to the treatment of the disease, but considering different criteria.

During treatment, markers like MRD can help to monitor disease evolution, but they shouldn't define treatment response. Although 2GENs lead to faster marker normalization, they don't improve PFS or OS. When one therapy is no longer more effective than the other, the focus must shift to economic costs and side effects. Indeed, 2GEN drugs like Nilotinib carry significantly higher long-term cardiovascular risks than imatinib [13]. Since safer alternatives exists, such a risk is no longer justified. Ultimately, treatment decisions should be based on clinical evidence, safety, and patient-centered considerations, not on fear, marketing pressure, or surrogate endpoints. Informed discussions with patients and shared decision-making are essential for optimizing adherence and ensuring that therapy aligns with both medical evidence and individual values [12].

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DATA AVAILABILITY

The data contained in this manuscript are available from the corresponding author upon request.

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AUTHOR CONTRIBUTIONS

CGP designed the experiment and wrote the manuscript. RGP supervised the project. GB took part in the experiment and helped write the manuscript. SB took part in the experiment and helped write the manuscript. FD took part in the experiment and helped write the manuscript. EL took part in the experiment and helped write the manuscript. AR took part in the experiment and helped write the manuscript. EM took part in the experiment and helped write the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the relevant guidelines and regulations. Ethical approval was not necessary for this type of research as no patient or patient derived materials were involved. For the same reasons no informed consent collection was possible.

ADDITIONAL INFORMATION

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