A significant proportion of patients with chronic myeloid leukemia and suboptimal response according to European Leukemia Net criteria have excellent prognosis without treatment change

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Background. The Recommendations of the European Leukemia Net (ELN) have become an essential tool in the management and prognosis of patients with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (TKIs). However, the definition of suboptimal response remains under discussion.

Methods. We used conventional cytogenetics for the detection of clonal changes in Ph-positive and negative clones. RT-PCR and sequencing were carried out on peripheral blood leukocytes to detect the type of *BCR-ABL1* transcript. The *BCR-ABL1* mutational status was assessed using sequencing of RT-PCR products. High performance capillary electrophoresis for determination of imatinib (IMA) plasma concentration was used.

Results. A retrospective study of 110 patients diagnosed with chronic-phase (CP) CML treated with IMA or 2nd generation TKIs in the years 2000-2009 focused on analysis of patients with suboptimal response according to ELN criteria. 40 patients were administered IMA as first-line therapy and 70 had been pretreated with interferon-alpha (IFN-α) with or without Ara-C and/or hydroxyurea (HU) for a median 12 months (range, 1-92 months). After adjusting for the ELN criteria, major molecular response (MMR) was achieved after median 34 and 39 months in 66.7% and 41.7% of patients after the first and second-line IMA therapy with suboptimal response defined as lack of achievement of MMR at the 18th month of treatment, respectively. In comparison to patients with optimal response, patients with suboptimal response did not show significant differences in overall survival (OS) or progression-free survival (PFS). Cytogenetic assays demonstrated additional chromosome abnormalities (ACAs): chromosome 8 trisomy in a Ph-negative clone during the IMA treatment (in 1 case) and der(9q) in Ph-positive clone (in 2 cases); in patients receiving first-line IMA only chromosome 8 trisomy was observed which was associated with myelodysplastic syndrome – this was the only case where hematopoietic stem cell transplantation (HSCT) was performed. During the treatment with IMA in both subgroups no regulatory mutations in the ABL kinase domain were confirmed.

Conclusion. We believe that the category of suboptimal response should be redefined or withdrawn from the ELN 2009 recommendations for management of CML patients treated with TKIs. Patients with suboptimal response who have no additional risks (additional cytogenetic abnormalities or *BCR-ABL1* regulatory mutations) may remain on IMA treatment while patients with these risks should be switched to the 2nd generation TKIs.

Key words: chronic myeloid leukemia, ELN recommendations, suboptimal response

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INTRODUCTION

The prognosis of patients with CML radically changed after 2000, when a completely new treatment with IMA entered clinical practice. The dramatically improved efficacy of IMA and later on, second generation TKIs necessitated the introduction of revised criteria for management and monitoring of CML patients. The Recommendations of the European Leukemia Net published first in 2006 and revised in 2009 gained very wide recognition and level of acceptance[1,2]. Response to treatment according to ELN criteria is divided into optimal, suboptimal and failure according to the achievement or failure to achieve CCyR and MMR at predefined time intervals (milestones).

While the definitions of optimal response and failure have shown clear prognostic value and implications for subsequent management of patients, the suboptimal response defined as failure to achieve CCyR at 12 months of treatment and MMR at 18 months recommended further treatment strategies that are more ambiguous: "suboptimal responders may continue on IMA, at the same or higher dose, or may be eligible for investigational therapy with 2nd generation TKIs[2]". Also the prognostic significance of suboptimal response was found to be limited and has been questioned[3].

In our retrospective study, we evaluated the significance of suboptimal response in two groups of patients with CP CML; first: 70 patients treated with second-line IMA

(pretreated with IFN-α) and second: 40 patients treated with IMA as front-line therapy. We approved the prognostic significance of suboptimal criteria according to ELN which is limited to event-free survival (EFS) only. We believe that the definition of suboptimal response should be revised and redefined or even withdrawn from ELN recommendations.

MATERIAL AND METHODS

Patient's characteristics

The analysis included all consecutive chronic-phase CML patients treated with first- or second-line IMA at the Department of Hemato-Oncology in Olomouc from 1st December 2000 to 1st May 2009. The group was analyzed as of 1st March 2010. IMA was administered to 40 patients as first-line therapy (from September 2001) and as second-line therapy to 70 patients previously treated with IFN-α with or without Ara-C and/or HU (from November 2000).

Treatment

The patients were given a daily dose of 400 mg of IMA. In cases of significant hematologic toxicity (National Cancer Institute grade III), treatment was rarely interrupted and intermittent dosage was mostly used[4]. In persistent neutropenia, G-CSF was administered in individual dosage regimens. Most patients had their plasma IMA levels monitored. If lower plasma IMA levels, suboptimal response or failure of therapy were noted, the drug dosage was individually increased to as much as 400 mg/day or 2nd generation TKIs were administered. In a minority of cases non-compliance was identified by the demonstration of lower plasma IMA levels.

Definition of treatment response

The ELN standard criteria were used (Table 1) (ref.[2]). Overall survival is defined as the interval from initiation of IMA therapy to the patient's death or the date of last analysis of the group (1st March 2010); duration of IFN-α pretreatment is excluded from the analysis to ensure proper comparison of both groups. Progression-free survival was also studied, with progression being defined according to the International Randomized Study of Interferon vs STI571 (IRIS) as acceleration, blast crisis, loss of complete hematologic response, loss of major cytogenetic response (MCyR), increasing white blood cell (WBC) count in patients who failed to achieve CHR and death. The last analyzed parameter was event-free survival, with an event being defined as progression, failure of IMA therapy (ELN), IMA intolerance and loss of CCyR, and failure to achieve MCyR by 12 months, MCyR by 18 months and CHR by 6 months of IMA therapy[5].

Statistical analysis

For descriptive statistics, the following basic parameters were used: continuous variables – the median, arithmetic mean, range and standard deviation; categorical variables – the frequency. Survival analysis was performed using the Kaplan-Meier method. Survival curves were compared by the log-rank test. The Mann-Whitney U test served to compare parameters that showed other than normal distribution (e.g. leukocyte subpopulations). Normality of the distribution was verified by the Kolmogorov-Smirnov test. The results were referred to as statistically significant at the level of significance of $P<0.05$. All calculations were carried out using the SPSS software (version 15.0 for Windows, SPSS Inc., Chicago, USA).

RESULTS

Basic characteristics

A detailed description of the group is provided in (Table 2). From the whole group of 110 patients, 104 individuals were alive as of 1st March 2010: in 5 cases, death resulted from progression of the disease and one patient died of a non-hematologic malignancy (laryngeal cancer).

The dosage of IMA in both first- and second-line therapy was standard (in 64.3% and 65.0% of patients, respectively) or increased to a maximum of 800 mg/day (in 27.1% and 27.5% of patients, respectively) or reduced to a minimum of 100 mg/day (in 8.6% and 7.5% of patients, respectively). In both subgroups, dosage was most commonly increased due to cytogenetic progression and reduced due to hematologic toxicity.

Table 1. ELN criteria for assessing treatment response in CP CML patients treated with IMA (ref.[2]).

Response	Time of assessment (months)				
	3	**6**	**12**	**18**	Anytime
Optimal	minCyR	PCyR	CCyR	MMR	Stable or improving MMR
Subopt.	No CyR	< PCyR	PCyR	< MMR	Loss of MMR; BCR-ABL1 kinase domain mutation sensitive to IMA
Failure	< CHR	No CyR	< PCyR	< CCyR	Loss of CHR; loss of CCyR; BCR-ABL1 kinase domain mutation low sensitive to IMA, ACAs in Ph-positive clone

Warnings include: high risk CML at the time of diagnosis, ACAs in Ph-positive clone and a rise of *BCR-ABL1* transcript anytime.

Table 2. Basic characteristics of the patients.

Parameter[a]	(IFN-α), 2nd line IMA	1st line IMA
No. of patients	N=70	N=40
Sex (male/female)	42/28	24/16
Age at dg. (years)	52 (18–71)	52 (19–73)
Age at IMA start (years)	56 (24-75)	52 (19–73)
Duration of IFN-α therapy	12 (1–92)	–
Duration of IMA therapy	64 (7–103)	41 (3–81)
Follow-up (from dg.)	85 (4–236)	43 (4–101)
Sokal index (L/I/H)	32/26/12	16/11/13
Treatment: IMA failure (dasatinib/nilotinib)	7/4	7/3
ELN criteria (O/S/F)	22/24/24	23/12/5

Legend: Sokal L/I/H – low/intermediate/high risk, ELN criteria (regardless of the time of assessment) O/S/F – optimal/suboptimal/failure, N – number of patients.

[a] Continuous variables are in the format of median (minimum-maximum) in months.

Patient's survival

The probability of 6-year survival was 95.4% in patients pretreated with IFN-α and 91.8% in first-line IMA therapy (this reflects the fact that deaths in this arm occurred within 15 months from the IMA start). The patients' survival was associated with the risk as expressed by ELN criteria. After adjustment by ELN criteria, statistically significantly better OS was seen in patients with optimal response (Fig. 1a, 1b). After 6-years follow-up, there was a statistically significantly lower ratio of progression in the optimal response subgroup (IFN-α pretreatment vs. first line IMA: optimal response 100% and 100%, respectively; suboptimal response 100% and 91.7%, respectively; failure 55.3% and 26.7%, respectively; $P<0.0001$ and $P<0.0001$, respectively) (Fig. 2a, 2b). Similar results were also obtained for EFS: optimal response 95.5% and 94.7%, respectively; suboptimal response 50.0% and 37.5%, respectively; failure 0% and 0%, respectively; $P<0.0001$ and $P<0.0001$, respectively) (Fig. 3a, 3b).

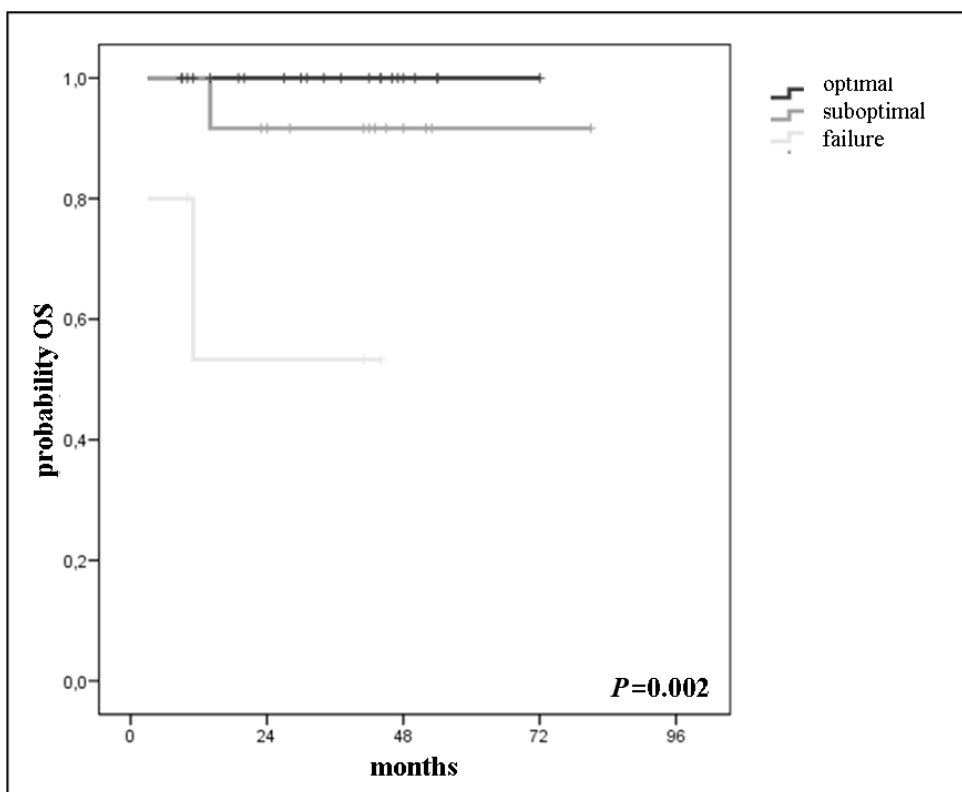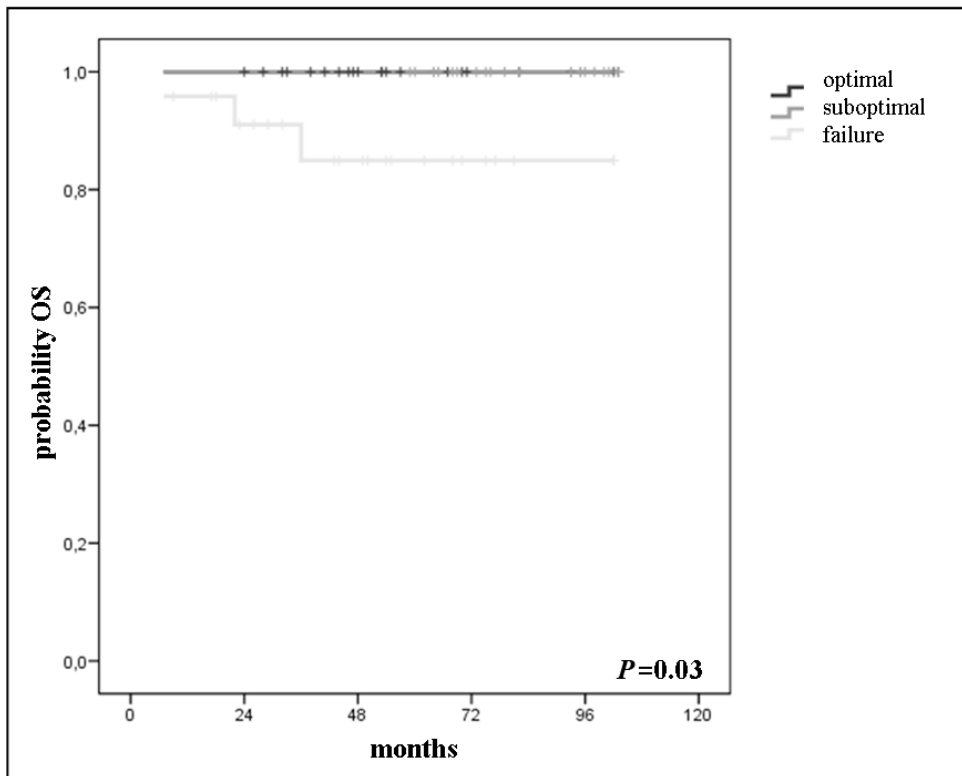## ELN criteria (suboptimal response) vs. molecular response

For an objective description of the treatment response achieved, the ELN criteria were used. We demonstrated that MMR was reached (IFN-α pretreatment vs. first line IMA): in 39 months (10 patients; 41.7%) and in 34 months (8 patients; 66.7%; $P=0.10$). This clearly shows that there were no statistically significant differences in the achievement of MMR with respect to pretreatment with IFN-α and also that all patients from the suboptimal response subgroup reached the CCyR. Cytogenetic assays in patients pretreated with IFN-α demonstrated ACAs: chromosome 8 trisomy in a Ph-negative clone during the IMA treatment (in 1 case) and der(9q) in Ph-positive clone (in 2 cases); in patients receiving first-line IMA only chromosome 8 trisomy was observed which was associated with the myelodysplastic syndrome – this was the only case where HSCT was performed. During the treatment with IMA in both subgroups no regulatory mutations in the ABL kinase domain were confirmed. We identified D276 mutation (in 2 cases) which is described as a silent mutation.

DISCUSSION AND CONCLUSION

Treatment responses in CML are defined according to hematologic, cytogenetic and molecular evaluations[2,6]. Milestones for suboptimal response and failure are different and several groups have developed guidelines defining inadequate response to IMA in patients with chronic phase CML based on failure to achieve specific levels of response within a defined duration of treatment[7-9]. We can estimate the rates of suboptimal response to IMA (defined by the ELN) using IRIS study data[10]. Using Kaplan-Meier curves for cumulative best response, approximately 88% of patients achieved CHR within 3 months, 69% achieved CCyR within 12 months and 62% achieved MMR within 18 months (calculated in patients with a CCyR) (ref.[11,12]). It is important to note that response rates achieved at each time point are cumulative and do not reflect patients who subsequently lost their response before reaching the milestone.

Potential mechanisms behind suboptimal response to IMA therapy are likely to be multi-factorial. It is important to distinguish *BCR-ABL1*-dependent and *BCR-ABL1*-non-dependent factors for understanding from a pathophysiological point of view; these factors may contribute jointly.

Fig. 1a. Overall survival in CML patients according to ELN criteria (IFN-α pretreatment).

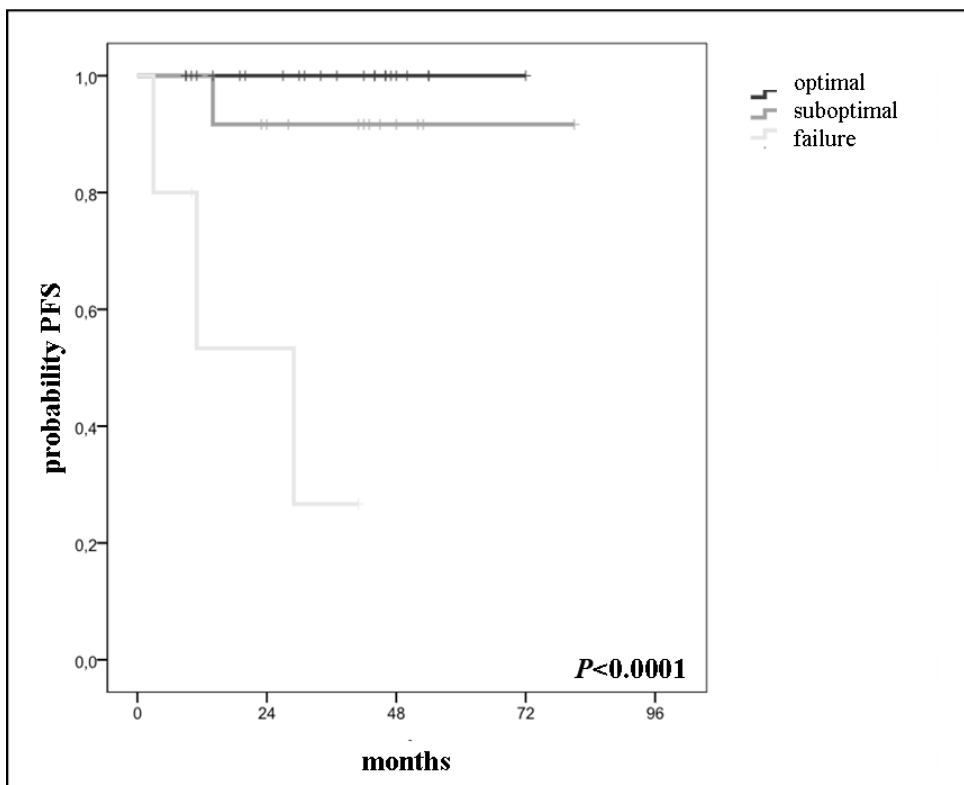**Fig. 1b.** Overall survival in CML patients according to ELN criteria (IMA 1st line therapy).

BCR-ABL1-dependent mechanisms involve amplification of *BCR-ABL1* gene and point mutations in the segment which encodes the *BCR-ABL1* kinase domain. The non-dependent mechanisms are associated with changes in extra- and intracellular levels of IMA and also with activation of other signaling pathways. The causes of resistance are summarized in (Table 3).

It seems that the categories, optimal and suboptimal response have in the case of OS and PFS a very similar stratification. Also pretreatment with IFN-α has not shown substantial impact for this parameter. Although the data are obtained from a relatively small group of patients, it clearly shows the inconsistency for classification into 3 different subgroups according to ELN criteria. Nevertheless, all patients with suboptimal response (assessed after 12 months) achieved CCyR and even a small
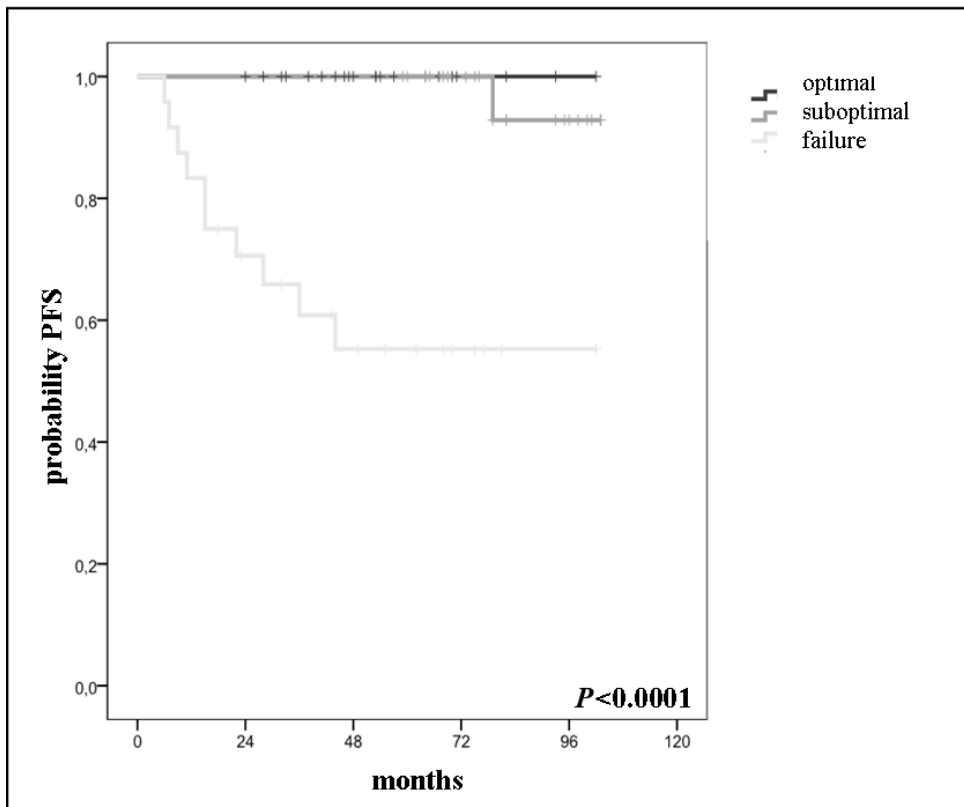
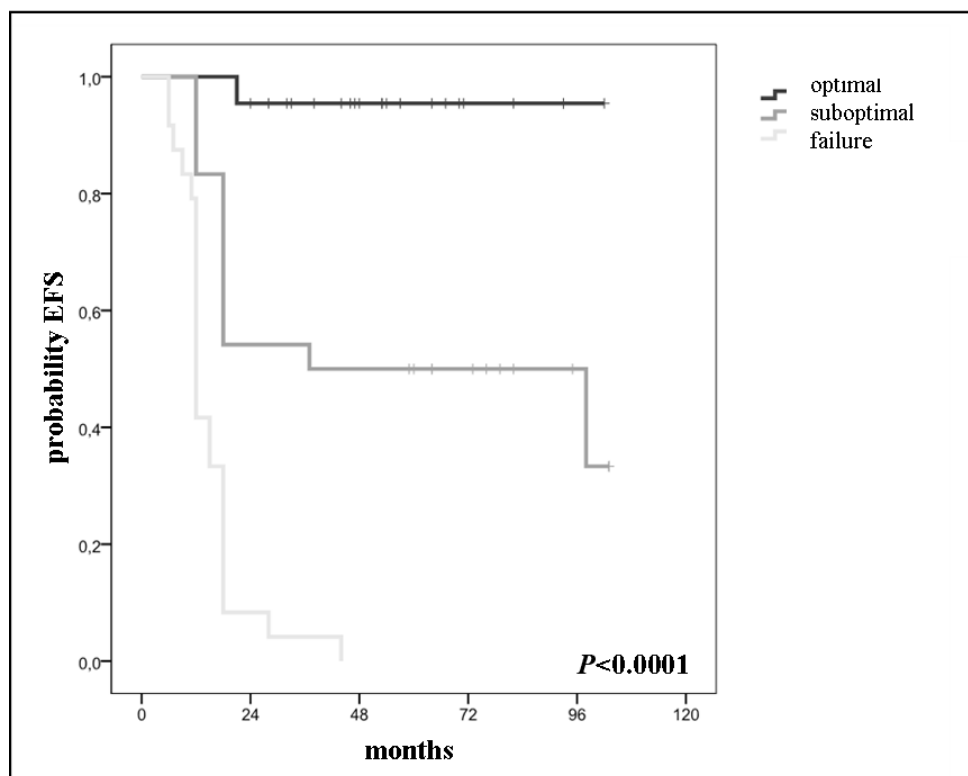**Fig. 2a.** Progression-free survival in CML patients according to ELN criteria (IFN-α pretreatment).

Fig. 2b. Progression-free survival in CML patients according to ELN criteria (IMA 1st line therapy).

number of patients who failed on IMA treatment (did not achieve CCyR after 18 months) eventually reached CCyR. A different situation appears in the case of EFS; for this parameter the ELN criteria of 2009 are useful and have a predictive value.

Patients with suboptimal response clearly form a heterogenous group: a significant proportion of them show image characteristics which correspond to the optimal response. It is therefore necessary to define the crucial parameters in the suboptimal group with a prognostic value[25]. According to the results of our retrospective analysis, we can certainly propose inclusion of the following criteria: the absence of ACA, the absence of mutations in the ABL kinase domain, improving molecular response

Fig. 3a. Event-free survival in CML patients according to ELN criteria (IFN-α pretreatment).
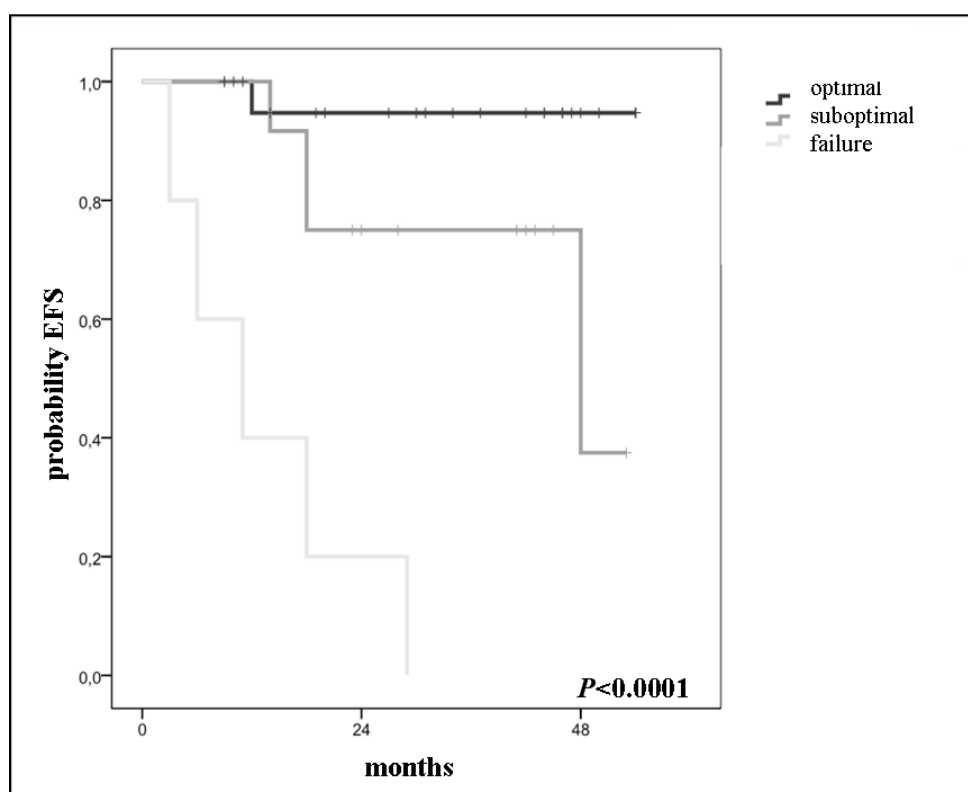
**Fig. 3b.** Event-free survival in CML patients according to ELN criteria (IMA 1st line therapy).

and standard dosage of IMA. The provisional guidelines for management of patients with suboptimal response are outlined in (Fig. 4).

Due to the small number of patients with ACAs it was impossible to statistically analyze their impact on OS. However, the published data suggest that there is probably no difference in survival between individuals with a single abnormality (Ph chromosome) and those with ACAs such as der(9q) deletion or chromosome 8 trisomy, i.e. almost all abnormalities seen in our group. Identification of a complex karyotype is a completely different case[22].

At present, interim criteria are available for assessing treatment with second-generation TKIs in chronic-phase CML patients resistant to IMA. These are more restrictive – suboptimal response: minCyR at 3 months, PCyR at 6 months, no MMR at 12 months; failure: noCyR at
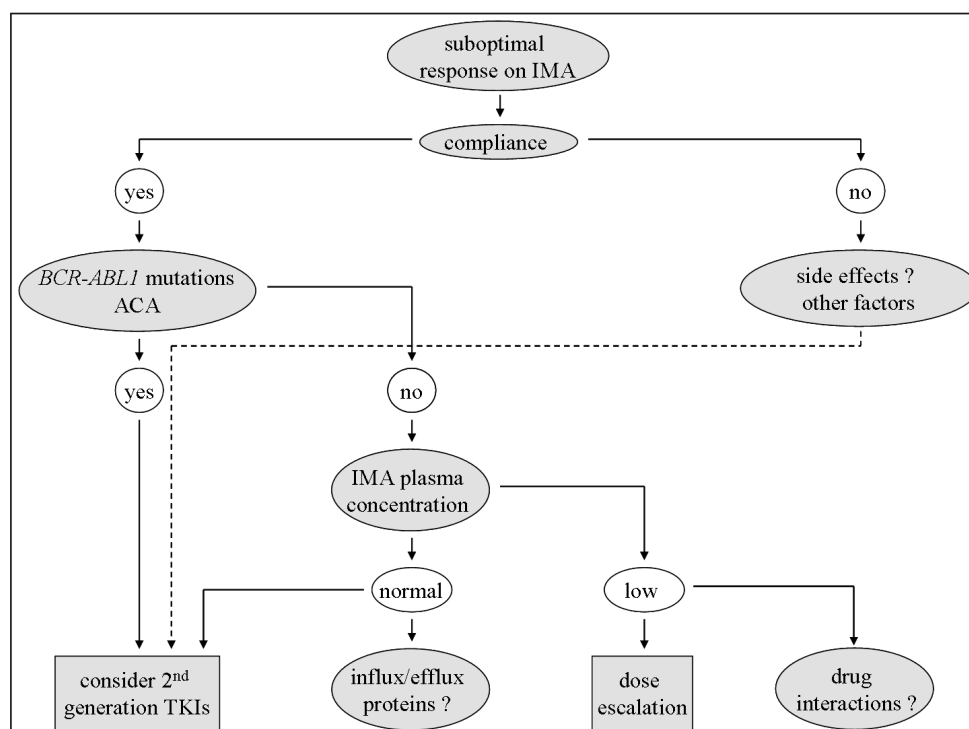
Fig. 4. Suboptimal response to IMA treatment - review of basic mechanisms and therapeutic options (modified from[26]).

months, minCyR at 6 months, no PCyR at 12 months) (ref.[2]).

The present study analyzed a group of chronic-phase CML patients treated in Olomouc, Czech Republic. The ELN criteria have an independent prognostic value for the OS, PFS and EFS but the future will necessitate revision,especially in regard to the category of suboptimal response.

ABBREVIATIONS

ACAs, Additional chromosome abnormalities; CCyR, Complete cytogenetic response (Ph-positive metaphases undetected); CHR, Complete hematologic response (normal blood count values – WBC count < $10x10^9$/L, less than 5% of basophils, normal differential WBC count without immature granulocytes, platelet count < $450x10^9$/L, nonpalpable spleen); CML, Chronic myeloid leukemia; CP, Chronic phase; CyR, Cytogenetic response; Dg., Diagnosis; EFS, Event-free survival; ELN, European LeukemiaNet; HSCT, Hematopoietic stem cell transplantation; HU, Hydroxyurea; IFN-α, Interferon-alpha; IMA, Imatinib mesylate; IRIS, International Randomized Study of Interferon vs STI571; MCyR, Major cytogenetic response; minCyR, Minimal cytogenetic response (reduction of Ph-positive metaphases to 66%); MMR, Major molecular response BCR/ABL to ABL ratio ≤ 0.1% of the international scale ; OS, Overall survival; PCyR, Partial cytogenetic response (Ph-positive metaphases 1–35%); PFS, progression-free survival; Ph, Philadelphia chromosome; TKIs, Tyrosine kinase inhibitors;WBC, white blood cell

Table 3. Analysis of resistance to IMA treatment[13-24].

- **Leukemic cell**
  - *BCR-ABL1*-dependent
    - ✓ amplification of *BCR-ABL1* gene
    - ✓ mutations in *BCR-ABL1* gene
  - *BCR-ABL1*-non-dependent
    - ✓ constitutive activation of other signaling molecules (e.g. SRC kinases)
    - ✓ multi-drug resistance (MDR-1)
    - ✓ changes in cellular efflux/influx pumps
    - ✓ additional cytogenetic abnormalities in Ph-positive clone
- **Extracellular**
  - ✓ immunologic factors
  - ✓ α1-acid glycoprotein
  - ✓ low IMA plasma level

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