CML AdvocatesNetwork

EUROPEAN HEMATOLOGY ASSOCIATION

23RD CONGRESS

FRIDAY, JUNE 15, 17:30 - 19:00

BIOLOGY AND TRANSLATIONAL RESEARCH.
POSTERS. POSTER AREA.

Abstract: PF359

INHIBITION OF NUCLEOCYTOPLASMIC EXPORT ENHANCES SELECTIVE ELIMINATION OF LEUKEMIC STEM CELLS IN CHRONIC MYELOID LEUKEMIA

Prof. Michael DEININGER

Aims

Test whether reliance on NCE extends to LSCs, the reservoir for persistent CML.

Conclusion

Our data illustrates that interrupting NCE by SINEs preferentially eliminates CML LSCs and enhances their sensitivity to TKIs, suggesting that combinations of TKI and SINEs represent a clinical strategy to target BCR-ABL1 independent resistance, as well as persistent residual CML. Mechanistic studies exploring the effects of nuclear entrapment of certain NCE cargo proteins of biological significance in CML LSCs are ongoing and will be reported.

FRIDAY, JUNE 15, 17:30 - 19:00

BIOLOGY AND TRANSLATIONAL RESEARCH. POSTERS. POSTER AREA.

Abstract: PF360

IMMUNOMODULATORY EFFECTS OF IFN-ALPHA ON T AND NK CELLS IN CHRONIC MYELOID LEUKEMIA PATIENTS IN DEEP MOLECULAR RESPONSE IDENTIFY POTENTIAL CANDIDATES FOR TREATMENT DISCONTINUATION

Massimo Breccia

Aims

In order to better identify potential candidates of successful treatment discontinuation, we have examined the phenotypic and functional host immune compartment - in particular T cells, NK and NK cell subsets - by comparing patients who had received INFα prior to TKI treatment (IFNα+TKI) with patients treated only with TKIs (TKI-only).

Conclusion

Our data indicate that in CML patients treated with INFα+TKI, IFNα appears to induce substantial modifications in the immune system, in particular in memory T lymphocytes, differentiated NKG2C^{+} "long-lived" NK cells and DNAM-1^{+} "adaptive" NK cell responses, even after a long time period (12-17 years) from the last IFNα contact. Our results confirm that IFNα modulates and potentiates the host immunologic compartment and pave the way to design and carry out immunotherapeutic strategies aimed at maintaining a DMR after TKI discontinuation in CML patients.

FRIDAY, JUNE 15, 17:30 - 19:00

BIOLOGY AND TRANSLATIONAL RESEARCH. POSTERS. POSTER AREA.

Abstract: PF361

IDENTIFICATION OF GENES DIFFERENTLY EXPRESSED BETWEEN BONE MARROW CD34+/LIN- CELLS OF PATIENTS WITH CHRONIC-PHASE CHRONIC MYELOID LEUKEMIA AT DIAGNOSIS VS. 12 MONTHS OF FIRST-LINE NILOTINIB TREATMENT

Dr. Alessandra Trojani

Aims

In the contest of the REL-PhilosoPhi34 study (EudraCT: 2012-005062-34) on behalf of the Rete Ematologica Lombarda, we undertook gene expression profiling (GEP) of selected bone marrow (BM) CD34+/lin- cells of 30 patients with CP-CML at diagnosis vs. the same patients after 12 months of nilotinib treatment **to investigate molecular signatures characterizing both conditions.**

Conclusion

GEP analyses of CD34+/lin- cells of CP-CML patients at diagnosis vs. 12 months of nilotinib demonstrated that 264 genes belonging to 14 pathways **were significantly differently regulated**. We can speculate that nilotinib might interfere with biologic mechanisms (lipid and glycemic metabolism, insulin resistance, coagulation cascade and platelet activation) that are relevant in CML patients as previously determined by several studies in literature. The alteration of pathways regarding apoptosis in CML CD34+/lin- cells at diagnosis may underlie the increased cell proliferation playing a significant role in recognizing resistance mechanisms of leukemic stem cells treated with TKI. Future GEP studies on a larger cohort of CML patients at diagnosis vs. 12 months of nilotinib are ongoing. We believe that BM CD34+/lin- cells from CML patients at diagnosis and after nilotinib harbor differences in certain biologic and genetic properties, that may predict how well they will respond to nilotinib and we will test this hypothesis.

FRIDAY, JUNE 15, 17:30 - 19:00

BIOLOGY AND TRANSLATIONAL RESEARCH. POSTERS. POSTER AREA.

Abstract: PF362

NK-CELLS AND LOSS OF MOLECULAR RESPONSE AFTER TKI DISCONTINUATION IN CML PATIENTS

Nikolay Kapranov

Aims

The aim of the study is to estimate relations between different NK-cell subsets and *BCR-ABL* level in CML patients after TKI discontinuation.

Conclusion

These results show correlation between cytokine-producing NK cells and *BCR-ABL1* level, which potentially could be the evidence of participation of NK cells in the development of molecular relapse after TKI therapy discontinuation.

Abstract: PF363

LMC-TRIO, A REAL LIFE STUDY OF CHRONIC MYELOID LEUKEMIA CARE IN FRANCE BETWEEN 2006 AND 2013: FACTORS OF FAILURE FROM TREATMENT-FREE REMISSION

Canet Jim

Aims

In this study, we aim to investigate in a real life setting the factors influencing the failure of patients in TFR during its establishment. Population characteristics and care have been described according to their TFR status. In addition, we will describe the nature and the effect of factors leading to failure of TFR.

Conclusion

Despite the low numbers, our study shows that factors influencing the failure of TFR in a real life setting are comparable to those identified in clinical studies. In addition, our study points out the eventual role of the care facility that need further investigations.

FRIDAY, JUNE 15, 17:30 - 19:00

BIOLOGY AND TRANSLATIONAL RESEARCH. POSTERS. POSTER AREA.

Abstract: PF364

POLYMORPHISMS IN MULTIDRUG RESISTANCE TRANSPORTER GENES AFFECT THE DURATION OF MOLECULAR RESPONSE TO NILOTINIB IN CHRONIC MYELOID LEUKEMIA PATIENTS

Aims

We investigated the impact of 5 single nucleotide polymorphisms (SNP) in three ABC transporter genes, namely *ABCC1*, *ABCC2,* and *ABCB1,* on achieving and maintaining molecular response (MMR, DMR) in CML patients treated with nilotinib.

Conclusion

Our study hypothesizes, for the first time, that genetic variants in ABC genes may increase the number of patients not able to maintain a sustained MR3 with Nilotinib, thus limiting the number of patients able to achieve treatment-free remission. Further studies in lager series are warranted to confirm our preliminary experience.

Abstract: PF365

MYELOID CELL POPULATION DYNAMICS IN TKI-TREATED CML

Dr. Sieghart Sopper

Aims

Determination of myeloid cell populations in plasma of newly diagnosed CML-CP patients in the course of tyrosine kinase inhibitor therapy and definition of immunological surrogates for response prediction in CML-CP patients.

Conclusion

Our comprehensive study demonstrates that several myeloid cell populations are substantially altered in CML patients. Specifically, a low HLA-DR expression on monocytes, associated with immunosuppressive functions, may have a negative impact on anti-leukemic immune response and may constitute a biomarker for response prediction to TKI therapy.

FRIDAY, JUNE 15, 17:30 - 19:00

BIOLOGY AND TRANSLATIONAL RESEARCH. POSTERS. POSTER AREA.

Abstract: PF366

THE EFFECT OF PREGNANE X RECEPTOR SNP AND TKI TROUGH CONCENTRATION ON CLINIC RESPONSE AND TOXICITY AMONG CHINESE CML PATIENTS.

Zhiping Jiang

Aims

To study the correlation between trough concentration and drug effect including toxicity and clinic response among Chinese CML patients. To investigate the possible pharmacogenetic variation that could affect the IM metabolism then influence the clinic response or drug toxicity.

Conclusion

This finding suggests nuclear receptors affect clinic response of imatinib by interfering drug metabolism andhighlights the importance of investigation on the effect of nuclear receptors on TKI response among large cohort of CML patients.

Abstract: PF367

WT1 EXPRESSION PREDICTS THE RESPONSIVENESS OF CHRONIC MYELOID LEUKEMIA TO FIRST LINE THERAPY OF TYROSINE KINASE INHIBITOR

Eleonora Toffoletti

Aims

The aim of our study was to investigate the WT1 expression levels at onset and the response to first line TKI, in CML patients.

Conclusion

In our cohort, WT1 expression levels, at onset, were shown to be correlated with the response to TKIs. Moreover, our data confirm the correlation between b2a2 rearrangement and the unfavorable response. Finally, the level of 100 copies of WT1 on 10000 ABL copies seems to be a crucial cut-off to guide the physician in therapy administration and CML monitoring.

SATURDAY, JUNE 16, 17:30 - 19:00

BIOLOGY AND TRANSLATIONAL RESEARCH. POSTERS. POSTER AREA.

Abstract: PS1109

ENRICHMENT OF ASXL1 PATHOGENIC VARIANTS AMONG PRIMARY REFRACTORY CML PATIENTS

Kristin Gustafsson

Aims

To evaluate whether pathogenic variants in genes are enriched at the time of diagnosis in primary refractory CML patients negative for mutations in the *ABL1* kinase domain evaluated with next generation sequencing.

Conclusion

Detection of additional molecular abnormalities at the time of diagnosis especially in the *ASXL1* gene among patients with CML in chronic phase may be associated with primary resistance to the TKI treatment. Alternative therapeutic approaches should be considered for these patients.

Abstract: PS1110

THE PIVOTAL ROLE OF INSULIN-LIKE GROWTH FACTOR PATHWAY AS A THERAPEUTIC TARGET IN ABL TYROSINE KINASE INHIBITOR RESISTANT LEUKEMIA CELLS

Dr. Seiichi Okabe

Aims

Insulin-like growth factor (IGF) cause intracellular signaling that ultimately results in cellular growth and proliferation. Because IGF signaling pathways have crucial functions in hematological malignancies and solid tumors, IGF pathways may regulate ABL TKI sensitivity and drug resistant.

Conclusion

The IGF signaling pathway is involved in ABL TKI sensitivity and drug resistant in CML cells. We also provide the promising clinical relevance as a candidate drug for treatment of ABL TKI resistant leukemia patients.

SATURDAY, JUNE 16, 17:30 - 19:00

BIOLOGY AND TRANSLATIONAL RESEARCH. POSTERS. POSTER AREA.

Abstract: PS1111

ASXL1 MUTATIONS ARE FREQUENT IN CHRONIC MYELOID LEUKEMIA PATIENTS RESISTANT TO TYROSINE KINASE INHIBITORS BUT NOT IN PATIENTS WITH OPTIMAL RESPONSE

Mr. Marcin Machnicki

Aims

We and others previously reported an incidence of somatic mutations in myeloid-associated genes in cml patients progressing to cml-bp. Here, we aimed to assess prevalence of those mutations in a group of 23 patients with tki-res (as confirmed by loss of molecular and/or cytogenetic response according to eln criteria) and compare this group with our previously reported cohort of 36 cml patients, who reached major molecular response (mmr) within 6 months from the start of treatment and remained in mmr for at least 4 years.

Conclusion

According to several reports, *ASXL1* is one of the most commonly mutated genes in CML besides *BCR/ABL1*itself. Our data indicates that inactivating mutations in *ASXL1* may precede clinical resistance or emerge with the TKI-resistant clone. This emphasizes the potential biological importance of somatic mutations in epigenetic regulators such as *ASXL1* in the resistance to TKI. Further studies in terms of patient cohorts extension as well as verification of detected mutations in diagnostic samples are warranted.

SATURDAY, JUNE 16, 17:30 - 19:00

BIOLOGY AND TRANSLATIONAL RESEARCH. POSTERS. POSTER AREA.

Abstract: PS1112

THE UNCOVERING OF A BCR-ABL1 TYROSINE KINASE-INDEPENDENT SIGNATURE REVEALS NEW POTENTIAL THERAPEUTIC TARGETS IN CHRONIC MYELOID LEUKAEMIA STEM CELLS

Eduardo Gomez-Castaneda

Aims

To uncover BCR-ABL1 TK independent mechanisms in CML LSCs and target these to eradicate CML LSCs.

Conclusion

CML LSCs have de-regulated gene expression that is not corrected by TKI treatment, further supporting the hypothesis that CML LSCs have TKI-independent pathways contributing to TKI persistence. We have shown that targeting these proteins leads to a decrease in the number of CML $CD34^+$ cells and in the number of CFC. Taken together, our work confirms the existence of the BCR-ABL1 TK independent signature in CML LSCs and represents an avenue for novel therapy in CML.

Abstract: PS1113

OPTIMAL TIME POINT FOR BCR-ABL1 KD MUTATION ANALYSIS IN CML PATIENTS; BASED ON 2013 ELN GUIDELINE

Young Rok Do

Aims

To determine appropriate timepoints for mutation analysis, the frequency and type of BCR-ABL1 kinase domain mutation were analyzed using Sanger sequencing and were assessed by achieving landmark responses at specific timepoints.

Conclusion

We conclude that some patients with treatment failure, especially with cytogenetic criteria, should be warranted for mutation analysis. In addition, the majority of patients with warning criteria may be enough only with a close monitoring without routine mutation analysis. However, as a few patients with optimal response had mutation, mutation analysis should not be totally excluded.

SATURDAY, JUNE 16, 17:30 - 19:00

BIOLOGY AND TRANSLATIONAL RESEARCH. POSTERS. POSTER AREA.

Abstract: PS1114

CLONAL SELECTION DETERMINES RESULTANT DOMINANCE OF TYROSINE KINASE INHIBITOR-RESISTANT CELLS IN CHRONIC MYELOID LEUKAEMIA

Benjamin Leow

Aims

To determine the effect of various TKI resistance mechanisms on the survival of a BCR-ABL+ leukaemic cell population, over the course of increasing TKI exposure and treatment withdrawal. To examine TKI cross-resistance and find novel treatment strategies to target TKI resistant cells.

Conclusion

In a therapy resistant context, flux in clonal cell populations leads to shifts in sensitivity to TKI therapy. Our model, recapitulating several relevant resistance mechanisms, enables an accurate description of the dynamics of drug resistance in future research.

Abstract: PS1115

WT1 ANALYSIS IN CHRONIC MYELOID LEUKEMIA (CML) PATIENTS

Sabrina COLUZZI

Aims

The aim was to investigate the role of WT1 in CML outcome and prognosis.

Conclusion

In our study cohort, WT1-H patients seem to have a worse outcome than WT1-L, in terms of failure free survival and molecular response: 52% of WT1-H patients vs 13% of WT1-L patients had failure and needed to change therapy. So, WT1 could be a prognostic marker at onset. We suppose that WT1-H effect could be neutralized by correct use of second generation TKI. However, we need to study a larger number of patients to confirm this hypothesis.

Abstract: PS1116

DIGITAL DROPLET PCR MAY BETTER IDENTIFY CANDIDATES FOR TREATMENT DISCONTINUATION IN CHRONIC MYELOID LEUKEMIA REGARDLESS OF MEDIAN TREATMENT DURATION

Gioia colafigli

Aims

To evaluate the feasibility of ddPCR evaluation in CML patients who have reached a DMR, in order to verify the advantage in terms of LOD and LOQ, to validate the test and to propose the quantification of residual transcript amounts as an alternative test prior to discontinuation.

Conclusion

Our results suggest that ddPCR could be superior in terms of quantification of low levels of residual disease without the need of a calibration curve, as compared to classic RQ-PCR, in the same clinical conditions. In our cohort, considering any ddPCR positivity we could detect 42% of patients with a likely presence of minimal residual disease, suggesting that this tool increases the likelihood of identifying patients who could (or not) attempt TKI discontinuation within patients with an undetectable MR4.5, independently of the median time of treatment and of a stable DMR.

Abstract: PS1117

FREQUENCY OF TYPICAL AND ATYPICAL FUSION TRANSCRIPTS IN PATIENTS WITH BCR-ABL1-POSITIVE LEUKEMIAS – A SINGLE INSTITUTION STUDY

Aims

To determine the incidence of typical and atypical transcripts in a large cohort of patients with *BCR-ABL1* leukemias.

Conclusion

Our study further confirms the extreme heterogeneity of *BCR-ABL1* positive leukemia patients, as detected by qualitative RT-PCR. In CML, atypical *BCR-ABL1* rearrangements, although rare, account for 2.1%, and raise several practical issues concerning their monitoring and frequently non-optimal response to the applied therapy.