Results: Our results show that Everolimus induced a reduction in cell lines viability, with an IC50 of 20μM for sensitive cells and 25μM for Imatinib resistant cell lines. The cell death was induced by apoptosis and this drug has also an antiproliferative effect through an arrest in cell cycle progression in G1/G0. In ex-vivo studies, Everolimus reduced cell viability by increasing apoptosis of hematopoietic CD34+cells without cytotoxicity to lymphocytes. In the dose of 25 μM this mTOR inhibitor induced in CD34 cells an increase of 19% of these cells positive to annexin V compared with control, and only 8% of lymphocytes are in apoptosis. Comparing the response to TKI treatment with a previous study to Everolimus, we observed a tendency to higher efficacy in patients with cytogenetic response (CR) comparing with patients under molecular response (MR) (24.5% vs 18.7% of CD34 cells positive to annexin V). When compared patients under Imatinib treatment versus patients treated with 2nd or 3rd generation TKI, we observed a better response to Everolimus in the second group, also associated with lower toxicity to lymphocytes.

Summary/Conclusions: Our results reveal the efficacy of Everolimus in inducing cell death in CML cells, without cytotoxicity to normal cells, suggesting that Everolimus could be an alternative targeted therapeutic approach to CML patients. However, it is important to increase the number of patients in the study to confirm our results.

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PB1820
EFFECTIVITY AND SAFETY EVALUATION OF NILOTINIB AND DASATINIB (2G-TKI) ON FIRST LINE TREATMENT IN 73 PATIENTS WITH CML-CP OUTSIDE OF CLINICAL TRIALS. ANDALUSIAN CML REGISTRY (RALMC) JM Puerta1,2, A. Jiménez Velasco3, MC García4, JR Molina5, C. Ruíz6, C. Ferreñán7, MS Durán8, I. Simón9, E. Clavero9, MC Avellaneda9, A. Rosell9, I. Ballesteros9, S. Ramírez10, MA Portero10, MJ Ramírez10, M. Fernández10, M. Jiménez11, R. Pérez12
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Background: Even though they were approved last June 2011 to be used on first line, it is not a common procedure to begin treatment of CML-CP with 2G-TKI, despite it has been demonstrated its efficacy and safety against imatinib in ENESTnd and Dasision clinical trials.

Aims: To describe the RALMC experience in terms of efficacy and safety of 2G-TKI when used in CML-CP in Andalusia (Spain).

Methods: Descriptive analysis of 73 RALMC patients, treated from the outset in 18 hospitals of Andalusia (Spain) with nilotinib and dasatinib from June 2011 out of clinical trials. Results of BCR ABL are expressed in IS by means of Genio software, and are cataloged according to the 2013 ELN classification. Lineal dosage toxicity is recorded according to the 2013 ELN guidelines. Toxicity of each treatment, overall survival (OS), failure free survival (FFS), event free survival (EFS) and progression free survival (PFS) were evaluated. Deaths was defined as death from any cause, progression to accelerated phase (AP) or blast crisis (BC), loss of CCGR or MMR and change of treatment for any reason.

Results: Median of 49 years of age (18-78) and median of follow-up of 36 months (3-56). 59% male, 41% female. 54% low, 26% intermediate, 20% high Sokal index. 79% low, 21% high Eutos score (n 63). Treatment of first line: nilotinib 46 (63%), dasatinib 27 (37%). Probability of achieving CCGR at 6 months was 100% (54 of 54 evaluated patients). Probability of achieving MMR at 12 months was 85,7% (54 of 63 evaluated patients) and MMR at 18 months 93,4% (57 of 61 evaluated patients). In both branches of treatment, 77% of patients obtained rates of BCR ABL ≤1% (30 patients of 39 evaluated with nilotinib and 20 of 26 with dasatinib). Overall median value of BCR-ABL at 3 months was 0.16% (0.22 nilotinib, 0.15 dasatinib). Probability of achieving MMR in month 12 if BCR ABL in month 3 was <1 5% is of 94% as opposed to BCR ABL ≥1.5% which is 55% (p-value 0.001). Only one death is reported on the dasatinib branch (death related with CML). EFS with nilotinib was 85,5% and 74,4% with dasatinib. FFS with nilotinib was 89.9% and 86.1% with dasatinib. Both branches significantly differ in toxicity and progression in terms of EFS and FFS (p=0.28 and 0.73 respectively). No patient of the series progresses to AP or BC. 12 treatment changes are carried out; 5 due to toxicity (7%): 2 with nilotinib (1 neutropenia, 1 dermatological toxicity) and 3 with dasatinib (1 pleural effusion, 1 thrombocytopenia, 1 ocular thrombosis), 7 treatment changes due to lack of efficacy (9.5%): 4 failures due to CCGR loss, 2 dasatinib and 2 nilotinib (mutational study was positive with nilotinib: 1 E308V and 1 T315I mutation), 2 fails due to MMR loss (1 dasatinib, 1 nilotinib) and 1 change from nilotinib to dasatinib in month 9 due to warning.

Table 1.

| Table 1. 

Summary/Conclusions: The use of nilotinib and dasatinib as first-line treatment is consolidated as an excellent therapeutic alternative to CML-SP. Showing with our series the efficacy and safety of 2G-TKI, with high rates of cytogenetic and molecular response, deep and early, and low rates of toxicity without changing over treatment change. The cutoff point of BCR ABL in month 3 of 1.5% could determine the optimal response in month 12 as soon as they achieve MMR.

PB1821
OPTIMIZATION OF RADOTINIB DOSES BASED ON DOSE-EFFICACY AS WELL AS DOSE-SAFETY RELATIONSHIP ANALYSES FOR NEWLY DIAGNOSED PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA (CML)
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Background: Radotinib is a selective second generation BCR-ABL1 tyrosine kinase inhibitor approved for the treatment of chronic myeloid leukemia (CML). In the previous dose-safety relationship analyses (Leuk Lymphoma. DOI 10.3109/10428194.2015.1113278), a positive association was found between the radotinib dose adjusted for the patient’s body weight (Dose/BW) and the dose-limiting toxicity (DLT). Hence, a weight-based dosing method was suggested to improve the safety outcomes of radotinib.

Aims: To explore an optimal radotinib dosing regimen for the treatment of chronic phase (CP) CML based on the dose-efficacy as well as dose-safety relationship analyses.

Methods: The Phase 3 data were derived from a total of 160 newly diagnosed patients with CP CML treated with radotinib 300 mg BID or 400 mg BID (fixed dose regardless of BW). A logistic regression analysis was conducted to assess the impact of Dose/BW of radotinib on the achievement of major molecular response (MMR) (dose-efficacy relationship) or occurrence of DLT (dose-safety relationship) within 48 weeks of treatment. Subsequently, an optimal Dose/BW cut-off was selected based on chi-square tests and Kaplan-Meier analyses with log-rank test.

Results: Efficacy. A statistically significant inverse relationship was found between Dose/BW and the probability of achieving MMR when gender was controlled for (p=0.033). A significantly higher rate of MMR was achieved in patients who received <6.5 mg/kg than ≥6.5 mg/kg (56% vs 34%; chi-square test, p=0.045). Safety. A statistically significant positive relationship was found between Dose/BW and the probability of DLT occurrence (p=0.003). Among various Dose/BW cut-offs, the greatest difference in the rate of DLT occurrence was observed between patients who received <6.5 mg/kg and ≥26.5 mg/kg (57% vs 91%; chi-square test, p < 0.001) with the median time to first DLT being 194 days and 83 days, respectively (log-rank test, p < 0.001). Therefore, Dose/BW of 6.5 mg/kg BID appears to be a threshold dose of radotinib below which the efficacy is improved as well as the risk of toxicity is reduced.

Summary/Conclusions: The results indicate the need for dose adjustment of radotinib according to the patients’ individual BW. Based on the proposed cut-off of Dose/BW 6.5 mg/kg BID, the radotinib doses for patients weighing ≥60 kg and >600 mg/kg BID should be reduced to 300 mg BID and 200 mg/kg BID, respectively. A randomized well-controlled clinical trial would be needed to confirm the efficacy and safety of this weight-based dosing strategy.