TREATMENT- FREE REMISSION IN CHRONIC MYELOID LEUKEMIA -EXPERIENCE OF A SINGLE BRAZILIAN PRIVATE INSTITUTION USING IMATINIB COPIE

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Introduction: Evidence of several studies suggest that patients who have achieved a sustained stable deep molecular response (DMR) as MR4 and MR4.5 can be safely discontinued with close monitoring without relapse, despite BCR/ABL1 DNA remaining detectable. In Brazil, CML patients have received almost exclusively Imatinib as first-line treatment. However, in both scenarios there is a limit coverage of PCR exams/ year which allows for adequate monitoring but it is not sufficient for the implementation of TFR safely in eligible patients. **Aims:** To report a Brazilian single institution Imatinib discontinuation trial and to evaluate factors impacting treatment -free response (TFR) and treatment free survival (TFS) provided by own founds. **Methods:** From 2020 -2021, 26 eligible patients were invited to participate in a single arm trial of Imatinib discontinuation (DIP). Inclusion criteria: age > 18 years, chronic phase, minimum of 04 years of Imatinib therapy, deep molecular response sustained > or = 02 years (confirmed by 04 tests in the last two years, defined MR4.0 or MR 4.5 and a confirmatory exam at the moment of the screening). Atypical transcripts were excluded. After discontinuation, patients were monitored by RT- PCR monthly in the first year, every two months in the second year and every three months since the third year. Criteria for Imatinib re-initiation: loss of MMR confirmed by two exams, loss of cytogenetic response, loss of hematologic response, disease progression. TFR was calculated from the date of discontinuation until first event: loss of MMR, Imatinib reintroduction, death any cause or last follow up. TFS was calculated from the date of imatinib discontinuation until reintroduction or last follow- up (censoring deaths not related to CML). The costs of exams were provided by own founds of our institution. **Results:** From 26 patients, 20 patients agreed to consent inform to discontinuation of imatinib. 06 patients declined despite information because their insecurity about TFR. Twelve patients (60%) presented MR4. Median age was 52.3 years old and 13 (65%) were female. Median time diagnosis to discontinuation of imatinib 8.04(4.6-15.5) years. Twelve (60%) patients sustained TFR. Seven patients of twelve had presented MR 4 and five had MR 4.5 in the screening, respectively. (p = 0,85). It means 58,3% of the total of patients with MR 4 and 62,5% with MR 4.5. In this interim analysis the median time of follow up was 14.5 (2.7-18.8) months. One patient died due to COVID19 with major molecular response (MMR). Eight (40%) lost MMR and imatinib was restarted. In this group the median time until MMR loss was 7.24 (2.1-13.8) months. At this moment, 07 patients (87,5 %) recovered MMR. In addition, in this group 06 patients (75%) achieved the same level of MR with reintroduction of imatinib with median 5.2 (3.7-6.3) months. Regarding adherence, 4 (20%) had some absences in monthly medical consultations and 1(5%) missed follow-up. Fifteen tests (6.14%) were performed to confirm MR loss, however only in 8 tests (53.3%) were confirmed. In fact, 04 patients (33,33%) still in TFR because of the double confirmatory test. There was no transformation to advanced phases. Gender, age at de diagnosis, age at discontinuation, Sokal, BCR-ABL trasncripts type, duration of Imatinib therapy, duration of MR 4.0 or MR4.5 did not affect TFR. Withdrawal syndrome occurred in 05 patients (25%); 04 patients with grade 1 and 01 patient with grade 2, had been used corticosteroid for few days. **Conclusions:** The preliminary results of this trial demonstrated the feasibility and safety of Imatinib discontinuation, even using Brazilian copies, and the results were similar of that presented in another trials.

https://doi.org/10.1016/j.htct.2022.09.359

FINANCIAL IMPACT OF IMATINIB DISCONTINUATION IN BRAZIL – A PHARMACOECONOMIC STUDY IN CHRONIC MYELOID LEUKEMIA OF A PRIVATE INSTITUTION

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Introduction: Recent studies showed that tyrosine kinase inhibitors (TKI) treatment could be safely discontinued in a selected group of chronic phase (CP) chronic myeloid leukemia (CML) patients that achieved deep molecular response (DMR), making treatment-free remission (TFR) a new goal of therapy. The discontinuation of treatment in patients with sustained molecular response to MR4 or MR4.5, a practice that has been performed in other countries is not feasible in Brazil outside clinical trials because of the lack of coverage for performing RQ-PCR as recommended by the international guidelines. For all these aspects, it seemed essential to us to analyze the financial impact of TKI discontinuation, following strict monitoring criteria, and perform a projection of economic costs in a population of CML patients treated in first-line with imatinib eligible for discontinuation. **Aims:** To demonstrate the feasibility of coverage of Q-PCR to perform discontinuation of imatinib treatment on eligible patients [treatment free-response (TFR)] in Brazil based on the financial impact. **Material and Methods:** From 2020 -2021, 20 eligible patients from a single private institution in Brazil were invited to participate in a single-arm trial of Imatinib discontinuation (DIP). After discontinuation, patients were monitored by RT- PCR monthly in the first year, every two months in the second year, and every three months after the third year. Criteria for Imatinib re-initiation were the same of the Euro-Ski trial. Considering that US$ 1.00 are R$ 5.3 (Brazilian currency- March /2022) for Branded Imatinib – 400 mg/d, the monthly cost has been estimated at R$ 16,933.90 or US$

3,95.07 and the generic imatinib- 400mg/d monthly R$ 13,048.90 or US$ 2,462.05 (CEMED- March/2022). The unitary value for the Q-PCR exam has been estimated, with a large price range at R$ 1,311.25 (R$790.00 to R$ 2,159.00) or US$ 247.40. **Results:** Of 26 patients, 20 consent to discontinuation of imatinib. Twelve patients (60%) presented MR4. Median time diagnosis to discontinuation of imatinib 8.5 (4.6-15.5) years. Twelve (60%) patients sustained TFR. During the follow-up, 244 RQ-PCR were performed. The cumulative time without treatment was 224.5 months. The costs with Q-PCR were R$ 319,945.00 or US$ 60,366.98 (244 exams during follow-up (median time 14,4 months). The average time of months without treatment was 224.5 months. The cost of treatment without discontinuation would be R$ 4,131,871.60 or US$ 779,598.41 (Branded Imatinib) or R$ 2,929,478.05 or US$ 552,731.70 (imatinib copies). The saving on median time of follow-up (14.4 months) were **R$ 3,811,926.60** or US$ 719,231.43 (Branded Imatinib) or **R$ 2,609,533.05** or US$ 492,364.72 (imatinib copies). **Discussion:** Considering the methodology of Cost-Utility, the saving resulting from the discontinuation of treatment for 20 patients for 14.4 months despite the loss of MR of 40 % of patients were R$ 3,811,926.60 or US$ 719,231.43 (Branded Imatinib) or R$ 2,609,533.05 or US$ 492,364.72 (imatinib copies). The results show that if Q-PCR tests were available in clinical practice, within pre-established protocols, there would be equalization and adequacy with the international monitoring guidelines, and discontinuation protocols could be feasible in clinical practice. **Conclusion:** The possibility of discontinuation would have a huge financial impact on the Brazilian Health System, resulting in the economic viability of treating hundreds of patients and performing thousands of Q-PCR exams, creating a rational and balanced model of clinical efficacy coupled with basic sustainability premises of modern oncology.

https://doi.org/10.1016/j.htct.2022.09.360

EFICÁCIA NO MUNDO REAL DO TRATAMENTO COM MESILATO DE IMATINIBE EM PACIENTES COM LEUCEMIA MIELOIDE CRÔNICA FASE CRÔNICA

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Objetivos: Comparar as respostas moleculares com mesilato de imatinibe (MI) em primeira linha em pacientes com LMC-FC não inseridos em estudos clínicos e correlacionar com os resultados de estudos randomizados. **Material e métodos:** Entre 01/2007 e 01/2017, 227 pacientes com LMC-FC fizeram uso de MI primeira linha no serviço de Hematologia da FMUSP-SP. Estudo observacional, não controlado, não randomizado, retrospectivo e unicêntrico. Realizada monitorização quantitativa dos níveis séricos de *BCR-ABL1* a cada três meses ou até atingir RMM. Pacientes categorizados de acordo com o ELN 2013. **Resultados:** A mediana de início do uso de MI foi 1,7 meses. Dentre os 227 pacientes, 60,3% mantiveram o tratamento, enquanto 39,7% trocaram para segunda linha. As respostas moleculares precoces aos 3 e 6 meses e a RMM aos 12 meses atingidas foram: 74,2% (164/221), 65% (134/206) e 56,5% (105/186). O tempo mediano para atingir a RMM foi de 9 meses e o tempo mediano de seguimento foi de 7,3 anos. As respostas moleculares RMM, RM4.0 e RM4.5 foram: 89,8%; 67,2% e 51,1%. A sobrevida global, a sobrevida livre de progressão e a sobrevida livre de eventos dos pacientes que utilizaram exclusivamente MI foram de 91%, 91% e 85,1%. **Discussão:** A eficácia a longo prazo do MI foi destacada na publicação de 10 anos do estudo IRIS, na qual os pacientes tiveram SG de 83,3%, SLP de 92,1% e SLE de 79,6%; 93,1% alcançaram RMM e 63,2% RM4.5. Nos pacientes que alcançaram RMM aos 12 meses, a SG estimada em 10 anos foi de 91,1% vs. 85,3%. Após 10 anos estudo IV LMC, a SG e a SLP de todos os pacientes foram de 82% e 80%. Em 10 anos, as taxas de RCC de 77%, RM2.0 de 91%, RMM de 88%, RM4.0 de 83% e RM4.5 de 70%. Os pacientes que atingiram *BCR-ABL1* ≤10% aos 3 meses (68,5%), <1% aos 6 meses (61%) ou 0,1% aos 12 meses (54,7%), obtiveram melhor sobrevida do que aqueles que não obtiveram. No estudo TIDEL, verificou-se que os pacientes que alcançaram *BCR-ABL1* <1% aos 3 meses possuíam 94% de probabilidade de alcançar RMM até os 24 meses de tratamento, reduzindo para 62% em caso de *BCR-ABL1* entre 1 e 10% e 35% se BCR-ABL1 >10%. A SG em 2 anos foi de 94% e a SLP foi de 93%. O estudo DASISION mostrou que 64% dos pacientes tratados com MI atingiram *BCR-ABL1* ≤10% aos 3 meses; SG foi de 90% e SLP de 86%. No estudo ENESTnd, a SG de 91,7% e a SLP foi de 91%. Neste estudo, a proporção de pacientes que alcançaram a RMP aos 3 meses foi de 74,6%, aos 6 meses 65% e RMM aos 12 meses 56,5% foi superior às verificadas nos estudos clínicos randomizados, exceto pela taxa de RM4.5 que foi superior neste estudo. O tempo mediano para atingir a RMM foi menor do que o tempo necessário no estudo IV CML: 9 meses vs. 14,9 meses. Na nossa análise, a SG se assemelha ao resultado demonstrado no estudo IRIS. Os pacientes que atingiram RM profunda apresentaram vantagem significativamente estatística em relação à SLP e SLE e uma tendência à melhor SG. As taxas de SLP, SLE e SG foram 81,9%, 50,5% e 85,8%. As taxas de SLP e SG foram semelhantes às dos estudos ENESTnd e TIDEL, todavia superiores às encontradas nos estudos IRIS e IV LMC. **Conclusão:** Dados sobre a eficácia e a segurança do MI no mundo real são escassos e a análise do tratamento da LMC-FC na prática clínica possui informações importantes. Os resultados apresentados por esta coorte de pacientes brasileiros são similares aos dos estudos prospectivos e randomizados, demonstrando que o MI ainda é uma excelente opção terapêutica.

https://doi.org/10.1016/j.htct.2022.09.361

TREATMENT-FREE RESPONSE USING BRAZILIAN IMATINIB COPIES AS FIRST LINE -RESULTS FROM TWO PROSPECTIVE CLINICAL TRIALS

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