ULUSLARARASI HEMATOLOJI-ONKOLOJI DERGISI REVIEW International Journal of Hematology and Oncology

Current Problems in the Management of Chronic Myeloid Leukemia in Turkey

Fatih DEMIRKAN

Dokuz Eylul University Faculty of Medicine, Department of Hematology, Izmir, TURKEY

ABSTRACT

Although a large scale survey investigating the practice patterns of physicians for Chronic Myeloid Leukemia (CML) throughout Turkey is absent, there is an increasing enthusiasm on this subject after several years of experience with Tyrosine Kinase Inhibitors (TKI) therapy. Considering the problems in the management of CML patients, we can focus on deficiencies in the laboratory tests for diagnosis and monitoring, management of suboptimal response with imatinib therapy and conducting visit frequency of patients.

Keywords: Chronic myeloid leukemia, Tyrosine kinase inhibitors, BCR/ABL

ÖZET

Türkiyede Kronik Myeloid Lösemi Tedavisinde Güncel Sorunlar

Türkiye'de kronik miyeloid lösemi için tedavi uygulamalarını inceleyen geniş ölçekli bir anket çalışması yapılmamış olmasına rağmen uzun yıllardır tirozin kinaz inhibitörleri ile tedavi tecrübesi bu konuya ilgi duyulmasını sağlamaktadır. Kronik Miyelositer Lösemi (KML) hastalarının izlemindeki problemler göz önüne alarak, tanı ve monitorizasyon için kullanılan laboratuvar testlerindeki eksiklikler, imatinib tedavisine suboptimal yanıtın değerlendirilmesi, ve hastaların takiplerinde görülme sıklığının düzenlenmesi konuları değerlendirildi.

Anahtar Kelimeler: Kronik miyeloid lösemi, Tirozin kinaz inhibitörleri, BCR/ABL

INTRODUCTION

Imatinib mesylate, which specifically targeted the tyrosine kinase activity of the oncogenic proteins encoded by BCR/ABL1, dramatically modified the treatment of chronic myeloid leukemia (CML). The IRIS (International Randomized Study of Interferon and ST1571) trial, in which patients with CML in chronic phase (CP) were randomly assigned to receive imatinib or interferon alfa (IFN-α) plus cytarabine (Ara-C) established imatinib as the standard therapy.[1] With 8 years of follow-up on this study[2] a complete cytogenetic response (CCgR) was achieved in 83% of patients, with a projected 8-year event-free survival (EFS) of 81% and a projected overall survival of 85%. 17% of patients never achieved CCgR, approximately 15% achieved CCgR but eventually lost it, and, nearly 5% were intolerant to imatinib. The risk of progression to accelerated phase/blast crisis (AP/BC) was greatest in the first 3 years of treatment (approximately 3.3% at 18 months) and decreased with longer follow-up (<1% after 4 years). On the basis of IRIS data, 30% to 35% of patients would need to change therapy. Approximately 50% of patients who develop imatinib resistance will achieve CCgR with a second generation tyrosine kinase inhibitor (TKI), and the 2-year progression free survival (PFS) rate after therapy with these agents is 64% to 81%.[3,4] Considering all patients successfully treated with a subsequent TKI, nearly 90% of patients would be expected to be alive and in CCgR.[5] Two randomized studies comparing second generation TKIs (nilotinib and dasatinib) with imatinib as initial treatment showed that faster cytogenetic and molecular responses and lower transformation rates (AP/BC) can be achieved.[6,7] The success of second-generation TKI on the basis of long-term outcome in comparison to sequential TKI therapy requires additional study and longer follow-up.

Monitoring the response to imatinib requires blood counts and differentials, cytogenetics, and molecular testing for BCR-ABL1 transcript level and for BCR-ABL1 kinase domain mutations. According to latest European Leukemia Net (ELN) recommendations[8], cytogenetics, performed with chromosome banding analysis (CBA) of marrow cell metaphases, is required at 3 and 6 months, then every 6 months until a CCgR has been achieved and confirmed, then every 12 months if regular molecular monitoring cannot be assured, and always in instances of myelodysplastic features, suboptimal response, or failure. Marrow CBA is preferred to interphase fluorescent in situ hybridization (I-FISH), because the definition of different grades of CgR is based on CBA, and because I-FISH does not detect clonal chromosome abnormalities in neither Ph^+ nor Ph^- clones. However, once a CCgR has been achieved, if CBA of a sufficient number of marrow cell metaphases cannot be performed, or marrow cells cannot be sampled, I-FISH of blood cells can be used to monitor the completeness of CgR by using BCR-ABL1 extra signal, dual color, or dual fusion probes and by scoring at least 200 nuclei.[9] Real-time, quantitative polymerase chain reaction (qRT-PCR) assessment of BCR-ABL1 transcript levels is recommended every 3 months until a major molecular response (MMolR) has been achieved and confirmed then at least every 6 months. qRT-PCR should be performed on whole buffy-coat blood cells, and results should be expressed as a ratio of BCR-ABL to ABL (or other housekeeping genes) x 100%; converted to the international scale, the ratio ≤ 0.1% defined MmolR.[10] Mutational analysis is required before changing to other TKIs or other therapies.[8]

Current Practice in Management of CML

Response criteria and switching to an alternative treatment in CML requires the assessment of laboratory tests which should be reliable, available and standardized. Until recently, because of the absence of in-house cytogenetic laboratories in community hospitals and difficulties in transferring bone marrow material (technical and administrative problems) common practice was forgoing bone marrow aspiration procedure and performing peripheral blood FISH assays among non-academic physicians. Qualified university laboratories for marrow CBA are also not many and satisfying results could not be obtained by most academic physicians. Although commercial laboratories working under an agreement with community hospitals increased in number in recent years, qualification and standardization are still persisting problems for most of them. Laboratories performing qRT-PCR are still far from internationally accepted standardization.

Mutational analysis could be ordered from a few laboratories including the commercial ones.

Although a large scale survey investigating the practice patterns of physicians for CML throughout Turkey is missing; there is an increasing enthusiasm on this subject after several years of experience with TKI therapy. A recent questionnaire including 30 participants (unpublished data) could give us some information on this practice. At initial diagnostic confirmatory FISH or cytogenetics, 67% used their own hospital laboratory, 23% a commercial and 10% an outside teaching or university hospital laboratory. Preferred confirmatory tests were 21% FISH, 35% qRT-PCR, 44% cytogenetic analysis. Although this questionnaire neglected combinations of these tests, it is apparent that cytogenetic analysis performed at diagnosis is below 50%. For monitoring the response to imatinib 40% preferred cytogenetic analysis, 40% RT-PCR and 20% FISH analysis. Only 60% of the participants performed cytogenetic analysis at 3 and 6 months and then every 6 months as recommended by ELN, whereas 30% performed at every 6 months and 10% annually. There was a consensus by 83% for ordering RT-PCR at every 3 months until achieving MmolR and then at every 6 months. 25% of the participants were not familiar with testing for BCR-ABL kinase domain mutations or had never ordered the test. Others considered it according to ELN recommendations but in fact the test was ordered for few patients who had treatment failures with multiple TKI's or before considering allotransplantation. In practice, when choosing a second generation TKI for an imatinib resistant patient, co-morbidities were taken into account rather than considering existence of probable BCR/ABL mutations. In the case of suboptimal response, 65% of the participants preferred to switch to nilotinib or dasatinib while 19% did not change the 400 mg/daily imatinib dose and 16% increased the imatinib dose to 600 mg/daily and both evaluated the patient 3-6 months later.

Focus on Problems in the Management of CML Patients

Considering the problems in the management of CML patients in Turkey we can focus on the following issues; i) deficiencies in the laboratory tests for diagnosis and monitoring; ii) management of suboptimal response in CML; iii) conducting visit frequency of patients.

Importance of CCgR has been established very early at the time when IFN-α was the standard therapy for CML. Patients who achieved CCgR with IFN-α had a significant improvement in survival, with 78% alive after 10 years.[11] In the imatinib era, various studies supported the importance of CCgR. The few patients who remained completely Ph^+ at 3 months had a low probability of achieving a CCgR later on.[12] At 6 months, patients without any CgR ($Ph^+ > 95\%$) had a low chance of achieving subsequent CCgR (25%) and MMolR (12%), and patients who achieved a CCgR or partial CgR (PCgR) had a significantly better 5-year PFS, EFS, and OS.[13,14] At 12 months, a CCgR yielded superior results compared with a PCgR for 5-year PFS and OS, and a PCgR was always better than a less than PCgR.[14] After 18 months of imatinib therapy, the PFS (99%) and the OS (98%) of CCgRs were always superior to those of PCgRs (87% and 76%, respectively).[12,14,15] Thus, CCgR is the goal of therapy in CML. Based on these findings, recent ELN recommendations define suboptimal response and failure already at 3 and 6 months, respectively, in occurrences of cytogenetic resistance.[8]

Current practice in Turkey has some drawbacks for management of CML. If someone relies on FISH for cytogenetic response evaluation there is a potential to neglect early suboptimal responses and failures at 3 and 6 months and detect only failures at 12 months. There are many advantages of FISH, including fast results (reporting time less than 24 hours), the use of nondividing cells, greater sensitivity to detect an abnormality than conventional cytogenetics (1% vs. 5%), and the ability to evaluate more cells than in typical metaphase karyotyping. With appropriate probes, the cutoff value of I-FISH may be established at 1% for CCgR[9] but there are no controlled and shared definitions of CgR by I-FISH especially for minimal and partial cytogenetic responses. If the concentration of CML cells is very low, interphase FISH may not detect BCR-ABL, so it has limited use for detecting minimal residual disease. Beyond 12 months of follow-up, quantitative RT-PCR is the method of choice for monitoring patients for residual disease if the CCgR is achieved.

In the case of suboptimal response in cytogenetics, switching to a second generation TKI can be recommended. However, assessing the value of molecular response is more difficult. Initial reports from the IRIS trial suggested that, among patients with CCgR, patients who achieved MmolR by 12 months had a significantly better EFS probability than those without MmolR.[15] With additional data, this difference was no longer detectable according to the 12-month response, but patients who had MmolR had an improved EFS probability at 72 months (95%) compared with those who had CCgR but no MmolR (86%) when response was measured at 18 months.[16] The difference in probability of survival without transformation to accelerated phase or blast phase (AP/BP), although significant, was considerably smaller. Current recommendations by the ELN do not include inability to achieve MmolR or loss of MmolR as a criterion of treatment failure, and there are no studies showing that any intervention (e.g., dose increase, change to new TKI) in this setting improves the long-term outcome.[8,17] Minor fluctuations in BCR-ABL transcript levels are common in many patients and are not necessarily cause for major concern. Most patients in CCgR who experience a rise in BCR-ABL transcript levels will remain in stable CCgR, although the risk of progression is greatest among patients who lost or never achieved an MmolR and experienced a >1-log increase in BCR-ABL transcript levels.[18,19] Most overlooked point is the integrity of molecular and cytogenetic analysis tests and necessity to evaluate them as a whole. If cytogenetic analysis results in the registry of the patient is missing or unreliable, decision making by qRT-PCR at a later time would be difficult.

As CML is a disease treated by oral medication for an indefinite time, ensuring the consciousness of the patient about the disease is extremely important. Patient should come his outpatient clinic appointments on time and be aware of the importance of laboratory tests in monitoring the disease. Hematologist should attend every visit and explain the patient his or her opinion about the attitude of the disease.

CONCLUSION

For best patient care in CML, improvement and standardization of laboratory tests required for disease monitoring is necessary. To ensure the awareness about the deficiencies in management of CML, surveys investigating practice patterns are mandatory.

ACKNOWLEDGMENT

The author would like to thank, in alphabetical order, Kadir Acar, MD, Önder Arslan, MD, Ferit Avcu, MD, Sevgi Beştışık, MD, Elif Birtaş, MD, Yahya Büyükaşık, MD, Seçkin Çağırgan, MD, Harika Çelebi, MD, Türker Çetin, MD, İmdat Dilek, MD, Hakan Göker, MD, Zafer Gülbaş, MD, Emel Gürkan, MD, İbrahim Haznedaroğlu, MD, Osman İlhan, MD, İhsan Karadoğan, MD, Oral Nevruz, MD, Serdar Bedii Omay, MD, Gülsüm Özet, MD, Fahir Özkalemkaş, MD, Bahriye Payzın, MD, Deniz Sargın, MD, Özkan Sayan, MD, MD, Mehmet Sönmez, MD, Fahri Şahin, MD, Burhan Turgut, MD, Mehmet Turgut, MD, Ali Ünal, MD and Selim Yavuz, MD for their attendance to CML surveys.

REFERENCES

1. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 348: 994-1004, 2003.
2. Deininger M, O'Brien SG, Guilhot F, et al. International randomized study of interferon vs STI571 (IRIS) 8-year follow up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. American Society of Hematology 51st Annual Meeting, New Orleans, Louisiana, December 5-8, 2009: P1126.
3. Hochhaus A, Baccarani M, Deininger M, et al. Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. Leukemia 22: 1200-1206, 2008.
4. Kantarjian H, Giles F, Bhalla K, et al. Update On imatinib-resistant chronic myeloid leukemia patients in chronic phase (CML-CP) on nilotinib therapy at 24 months: Clinical response, safety, and long termoutcomes. American Society of Hematology 51st Annual Meeting, New Orleans, Louisiana, December 5-8, 2009: P1129).

5. Al-Kali A, Kantarjian H, Shan J, et al. Current event-free survival after sequential tyrosine kinase inhibitor therapy for chronic myeloid leukemia. Cancer 117: 327-335, 2011.
6. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 362: 2260-2270, 2010.
7. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 362: 2251-2259, 2010.
8. Baccarani M, Cortes J, Pane F et al. Chronic Myeloid Leukemia: An Update of Concepts and Management Recommendations of European LeukemiaNet. J Clin Oncol 27: 6041-6051, 2009.
9. Testoni N, Marzocchi G, Luatti S, et al. A prospective study in Ph_ chronic myeloid leukemia (CML) patients showing that interphase fluorescence in situ hybridization (I-FISH) is effective as conventional cytogenetics for definition of cytogenetic response to imatinib: Correlation with molecular response (A GIMEMA CML WP study). Blood 114: 4939-4943, 2009.
10. Branford S, Fletcher L, Cross NCP, et al. Desirable performance characteristics for BCR-ABL measurement on an international reporting scale to allow consistent interpretation of individual patient response and comparison of response rates between clinical trials. Blood 112: 3330-3337, 2008.
11. Kantarjian HM, O'Brien S, Cortes JE, et al. Complete cytogenetic and molecular responses to interferon-alpha-based therapy for chronic myelogenous leukemia are associated with excellent long term prognosis. Cancer 97: 1033-1041, 2003.
12. De Lavallade H, Apperley JF, Khorashad J, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol 26: 3358-3363, 2008.
13. Hochhaus A, O'Brien SG, Guilhot F, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia 23: 1054-1061, 2009.
14. Kantarjian H, O'Brien S, Shan J, et al. Cytogenetic and molecular responses and outcome in chronic myelogenous leukemia. Cancer 112: 837-845, 2008.
15. Druker BJ, Guilhot F, O'Brien SO, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 355: 2408-2417, 2006.
16. Hughes TP, Hochhaus A, Branford S, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: An Analysis from the international randomized study of interferon versus STI571(IRIS). Blood 116: 3758-3765, 2011.
17. Cortes J, Hochhaus A, Hughes T, Kantarjian H. Front-Line and Salvage Therapies With Tyrosine Kinase Inhibitors and Other Treatments in Chronic Myeloid Leukemia. J Clin Oncol 29: 524-531, 2011.
18. Kantarjian HM, Shan J, Jones D, et al. Significance of increasing levels of minimal residual disease in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in complete cytogenetic response. J Clin Oncol 27: 3659-3663, 2009.
19. Press RD, Galderisi C, Yang R, et al. A half-log increase in BCR-ABL RNA predicts a higher risk of relapse in patients with chronic myeloid leukemia with an imatinib-induced complete cytogenetic response. Clin Cancer Res 13: 6136-6143, 2007.

Correspondence

Dr. Fatih DEMİRKAN

Dokuz Eylül Üniversitesi Tıp Fakültesi

Hematoloji Anabilim Dalı

35340 İnciraltı, İzmir / TURKEY

Tel: (+90.232) 412 48 53

Fax: (+90.232) 412 48 46

e-mail: fatih.demirkan@deu.edu.tr