Original Article

Analysis of Demographic and Disease Characteristics of Patients with Chronic Myeloid Leukemia: A Single Centre Retrospective Analysis

Kronik Miyeloid Lösemili Hastaların Demografik ve Hastalık Özelliklerinin Analizi: Tek Merkezli Retrospektif Bir Analiz

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ABSTRACT

Background: Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder, characterized by overproduction of cells of the myeloid series with the presence of the Philadelphia chromosome (Ph). With the development of tyrosine kinase inhibitors (TKIs), treatment options for CML have changed significantly. A key role in assessing the survival and prognosis of CML patients is the reduction of the BCR-ABL burden with appropriate treatment in defined time. The aim of this study was to analyze the clinical and demographic characteristics of CML patients, as well as their treatment efficacy, side-effect profiles, treatment resistance and survival.

Patients and methods: This retrospective study was conducted on patients diagnosed with BCR-ABL positive CML in the Hematology Department of our hospital between 2010 and 2020. The clinical and demographic characteristics of CML patients were analyzed together with treatment efficacy, side-effects, resistance to treatment, possible complications and survival.

Results: Evaluation was made of a total of 59 patients, with the mean age of 55.59±14.48 years, and median total follow-up period of 33.9 [0.2-172.0] months. All patients were given imatinib as the first-line treatment. Two patients were included in a trial of imatinib cessation at another center. At 12 months after imatinib treatment, 53.3% patients achieved major molecular response (BCR ABL <0.1). As second generation TKIs, dasatinib was preferred in 14 (46.7%) patients and nilotinib was preferred in 15 patients (50%). At 12 months after 2nd line TKI treatment, 77.8% patients achieved major molecular response (BCR ABL <0.1). Blastic transformation was detected in three patients during follow-up.

Conclusion: The results of the current study demonstrated that treatment options, response rates and side-effects were all comparable with the results of other real-world studies. Larger patient-based studies are needed to cover the course of the disease and to better manage these patients.

Key words: CML, management, treatment

ÖZET

Amaç: Kronik miyeloid lösemi (KML), Philadelphia kromozomunun (Ph) varlığı ve miyeloid serideki hücrelerin aşırı üretimi ile karakterize klonal miyeloproliferatif bir hastalıktır. Tirozin kinaz inhibitörlerinin (TKİ'ler) gelişmesiyle, KML için tedavi seçenekleri önemli ölçüde değişmiştir. KML hastalarının sağkalımını ve prognozunu değerlendirmede anahtar rol, BCR-ABL yükünün, uygun tedavi ile tanımlanan zaman ve değerde azalmasıdır. Bu çalışmanın amacı, KML hastalarının klinik ve demografik özelliklerinin yanı sıra tedavi etkinliklerini, yan etki profillerini, tedavi dirençlerini ve sağkalımlarını analiz etmekti.

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Gereç ve Yöntem: Bu retrospektif çalışma, 2010-2020 yılları arasında hastanemiz hematoloji bölümünde BCR-ABL pozitif KML tanısı alan hastalar üzerinde gerçekleştirilmiştir. KML hastalarının klinik ve demografik özellikleri, tedavi etkinliği, yan etkiler, tedaviye direnç, olası komplikasyonlar ve sağkalım parametreleri ile birlikte analiz edildi.
Bulgular: Bu çalışmaya toplam 59 hasta dahil edildi. Ortalama yaş 55.59±14.48 (yıl) ve medyan toplam takip süresi 33.9 [0.2-172.0] aydı. Tüm hastalara ilk tedavi olarak imatinib verildiği görüldü. Başka bir merkezdeki imatinib kesilme çalışmasına iki hasta dahil edildi. İmatinib tedavisinden 12 ay sonra, hastaların %53.3'ünde majör moleküler yanıt elde edildi (BCR ABL <0.1). İkinci kuşak TKİ olarak 14 (%46,7) hastada dasatinib, 15 hastada (%50) nilotinib tercih edildi. İkinci basamak TKİ tedavisinden 12 ay sonra, hastaların %77.8'i majör moleküler yanıt elde etti (BCR ABL <0.1). Üç hastada, takipte blastik transformasyon saptandı.
Sonuç: Mevcut çalışmanın sonuçları, tedavi seçeneklerinin, yanıt oranlarının ve yan etkilerin, mevcut literatür sonuçlarıyla karşılaştırılabilir olduğunu göstermiştir. Hastalıkların seyrini daha iyi yönetmek ve tedavilerini düzenlemek için daha geniş popülasyonlu çalışmalara ihtiyaç vardır.

Anahtar kelimeler: KML, yönetim, tedavi

Introduction

Chronic myeloid leukemia (CML) is a malignant hematological disorder that usually begins as a chronic phase (CP) and then reaches the accelerated phase (AP) and blastic phase (BP) within a short time if not treated and ends with death after the overproduction of clonal myeloproliferative cells due to the Philadelphia chromosome (Ph) effect [1, 2]. The incidence has been reported as 1-2 / 100,000 cases and 15% of all newly diagnosed leukemia cases. Since tyrosine kinase inhibitors (TKIs) came into use as the main treatment strategy, it was found that life expectancy approached that of the general population and there was a significant improvement in survival [3, 4]. Until the early 2000s, the treatment protocols planned for CML were extremely limited, consisting of toxic, non-specific, and non-promising agents such as busulfan, hydroxyurea, and interferon-alfa. Although there has been great progress in CML treatment with the use of TKIs, allogeneic-hematopoietic stem cell transplantation (allo-HSCT) is still an important therapeutic alternative for TKI-resistant patients [5, 6]. The key point in evaluating the survival and prognosis of CML is that the BCR-ABL burden has decreased in the defined time and value with appropriate treatment [7]. There are many different TKIs that can be used for the treatment of chronic phase CML by evaluating comorbidity, intolerance, mutation status or loss of efficacy [8].

The International Randomized Study of Interferon and STI571 (IRIS) has shown that imatinib, a tyrosine kinase inhibitor, is effective in newly diagnosed chronic phase chronic myeloid leukemia (CML-CP). In the same study, 343 patients were followed cytogenetically for 18 months and it revealed that patients treated with imatinib achieved a higher and sustained response than patients treated with interferon (IFN) plus cytarabine. The rate of complete cytogenetic response (CCyR) was 76% in imatinib arm and 15% in interferon (IFN) plus cytarabine arm [9].

Second-line therapy with nilotinib, dasatinib or bosutinib may provide high response rates in patients who have insufficient response to imatinib or who have been discontinued due to imatinib intolerance [10-12]. Ponatinib is a 3rd generation TKI option that is effective against all other TKI-resistant mutants including the BCR-ABL1 T315I mutation, which is also accepted as "gatekeeper", but can only be used in selected patients due to its high serious side-effects [13].

Table 1. Distribution of demographic characteristics and blood parameters of the patients

(N=59)	
Gender n (%)	
Female	29 (%49,2)
Male	30 (%50,8)
Age (year) Median [Min-Max]	55,0 [25,0-89,0]
Comorbidity n (%)	
No	36 (%61,0)
Yes	23 (%39,0)
Number of Comorbidities Median [Min-Max]	1,0 [1,0-4,0]
Hemoglobin (g/dL) Median [Min-Max]	11,3 [4,1-17,0]
WBC (×10^3/mm^3) Median [Min-Max]	68100,0 [5100,0-576500,0]
Neutrophil (×10^3/mm^3) Median [Min-Max]	52100,0 [3200,0-393000,0]
Platelet (×10^3/mm^3) Median [Min-Max]	298000,0 [64000,0-3803000,0]
Basophil (×10^3/mm^3) Median [Min-Max]	270,0 [0,0-25310,0]
Monocyte (×10^3/mm^3) Median [Min-Max]	2200,0 [200,0-28440,0]
LDH (/l) Median [Min-Max]	547,0 [152,0-2287,0]
Ferritin (ng/mL) Median [Min-Max]	69,5 [2,2-1119,0]
Vitamin B12 (pmol/L) Median [Min-Max]	925,5 [76,0-2000,0]

WBC:white blood cell, LDH: lactate dehydrogenase

The aim of this study was to analyze the clinical and demographic characteristics of CML patients, as well as treatment efficacy, side-effects, resistance to treatment, possible complications, and survival.

Patients and methods

This retrospective study was conducted on patients diagnosed with BCR-ABL positive CML in the hematology department of Diskapi Yildirim Beyazit Training and Research Hospital between 2010 and 2020. The diagnosis and classification of CML were made according to the WHO diagnostic criteria of myeloid neoplasms [14]. At the time of diagnosis, hematological, biochemical parameters and BCR-ABL IS levels were recorded. Demographic and disease characteristics of the patients, treatment management, complications, evaluation of the effect of planned treatment, distribution of first, second and next line treatment characteristics of patients, mutation analysis and follow-up periods were recorded for all patients.

Statistical analyses were performed using SPSS software (IBM SPSS Statistics 24). Frequency tables and descriptive statistics were used in the interpretation of the findings. All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and / or national research committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Approval for this study was given by the Local Ethics Committee (No: 107/2 Date: 22.03.2021).

Results

Evaluation was made of a total of 59 patients, comprising 30 (50.8%) females and 29 (49.2%) males with the mean age of 55.59 ±

Table 2. Distribution of findings regarding disease characteristics

(N=59)	
Splenomegaly	
No	24 (%40,7)
Yes	35 (%59,3)
Bone marrow blast at diagnosis (n=31)	
<%5	22 (%66,7)
%5-10	7 (%21,2)
>%10	4 (%12,1)
Eutos score Median [Min-Max]	12,0 [0,0-131,0]
Sokal score Median [Min-Max]	1,0 [0,6-20,0]
ELTSeutos score Median [Min-Max]	1,7 [0,7-3,2]
In diagnosis BCR-ABL IS (%) Median [Min-Max]	61,5 [0,0-291,4]
Total follow-up time (months) Median [Min-Max]	33,9 [0,2-172,0]
Final status	
Survivor	54 (%91,5)
Exitus	5 (%8,5)
Total follow-up time (months) Median [Min-Max]	33,9 [0,2-191,9]

Table 3. Distribution of patients' IMATINIB treatment characteristics

(N=59)	n (%)
BCR-ABL IS at 3rd month (n=42)	
≤10	28 (%66,7)
>10	14 (%33,3)
BCR-ABL IS at 6th month (n=39)	
≤1	27 (%69,2)
>1	12 (%30,8)
BCR-ABL IS at 12th month (n=30)	
≤0,1	16 (%53,3)
>0,1	14 (%46,7)
Adverse effects (n=8)	
Allergic rx-skin rash	2 (%18,2)
Nausea, vomiting, peripheral edema	1 (%9,1)
Drug eruption	1 (%9,1)
Leukopenia-skin rashes	1 (%9,1)
Pancytopenia	3 (%27,2)
Peripheral edema	2 (%18,2)
Cytopenia	1 (%9,1)
Total treatment duration Median [Min-Max], months	11,6 [0,0-87,7]

Table 4. Distribution of second and next line treatment characteristics of patients

(N=59)	n (%)
Reason for discontinuation of Imatinib (n=31)	
Inadequate response	19 (%61,3)
Adverse effect	10 (%32,3)
Discontinuation trial	2 (%6,4)
2nd line treatment type (n=29)	
Dasatinib	14 (%48,3)
Nilotinib	15 (%51,7)
BCR-ABL IS at 3rd months after 2nd line TKI (n=19)	
≤10	18 (%94,7)
>10	1 (%5,3)
BCR-ABL IS at 6th months after 2nd line TKI (n=17)	
≤1	15 (%88,2)
>1	2 (%11,8)
BCR-ABL IS at 12th months after 2nd line TKI (n=18)	
≤0,1	14 (%77,8)
>0,1	4 (%22,2)
Reason for discontinuation of 2nd line TKI (n=8)	
Inadequate response	4 (%50)
Adverse effect	4 (%50)
3rd line treatment type (n=8)	
Dasatinib	3 (%37,5)
Nilotinib	3 (%37,5)
Bosutinib	2 (%25)
Reason for discontinuation of 3rd line TKI (n=3)	
Inadequate response	3 (%100)
Adverse effect	-
4th line treatment type (n=3)	
Dasatinib	-
Nilotinib	-
Bosutinib	3 (%100)

14.48 years. At least one comorbidity was present in 23 (39.0%) patients. The distribution of demographic characteristics, hematological and biochemical parameters of the patients is shown in Table 1. The median total follow-up duration was 33.9 [0.2-172.0] months. At the last follow-up, 54 (91.5%) patients were survivors, and five (8.5%) patients were non-survivors. The median Sokal score was 1.0 [0.6-20.0]. Median BCR-ABL IS (%) at diagnosis was found to be 61.5 [0.0-291.4]. The distribution of findings related to disease characteristics is shown in Table 2.

All patients were given imatinib as the first-line treatment. Pancytopenia was seen as the most common side-effect leading to cessation of imatinib (n = 3, 27.2%). At 12 months after imatinib treatment, 16 patients achieved major molecular response (BCR ABL <0.1). The distribution of the first-line imatinib treatment characteristics of the patients is given in Table 3. During the follow-up, imatinib was discontinued in 19 patients due to insufficient response and in 10 patients for other reasons, and second generation TKIs were started. Two patients were included in the imatinib cessation trial at another center. Among the second generation TKIs, dasatinib was preferred in 14 (46.7%) patients and nilotinib in 15 patients (50%). Although MMR was obtained under imatinib treatment in one patient, unexpected ALL conversion was detected. Also transformation to blastic phase

(AML) was detected in two patients. The distribution of the second and next line treatment characteristics of the patients is shown in Table 4.

Discussion

With the development of TKIs, treatment options for CML patients have changed significantly. As imatinib and other next generation TKIs have become widely used, survival rates have also recently increased, to even reach similar levels to those of healthy subjects [15-17]. Due to the prolongation of survival, the management of side effects as well as optimal response to treatment has become increasingly important.

The main purpose of this study was to examine not only the clinical and demographic characteristics of the patients, but also their treatment preferences and responses, and to compare these with findings in the literature. In a previous real-life study conducted in Turkey for CML, median age was reported to be 46.1 ± 14.8 years [18]. In the current study, the median age at diagnosis of CML was 55.59 ± 14.48 years. However, this wide difference in the median age parameter has been demonstrated in many countries and studies [19]. Similar to national real data, there was no difference between male and female patient rates as 50.8% of the patients were female and 49.2% male [18]. In the current study, the median follow-up time was 33.9 months, and 39% of the patients had documented comorbidities, which was similar to CML Study IV [20]. There are findings stating that the presence of comorbidity negatively affects the prognosis of CML. In the CML STUDY IV where the median age was 56 years, at least one comorbidity was found in 55.5% of the patients diagnosed with CML in Europe, and in the current study, the average age was found to be similar and patients had at least one comorbid disease. Splenomegaly, which is known to be a common physical examination finding in CML patients has been detected in approximately 50% of cases in previous studies, and in the current study this rate was 59.3% [3].

All the current study CML patients received imatinib as the first treatment due to the national health insurance protocol. However, if it is possible, second generation TKIs can be used as the first choice in high-risk patients, and those who are young or need early deep response results [3].

The Grade 3-4 adverse events of neutropenia (17%), thrombocytopenia (9%) and anemia (4%) have been reported in many studies, and in the current study, pancytopenia (27.2%) was observed [21]. In CML long-term treatment, imatinib intolerance is considered an important treatment problem.

The IRIS study showed that approximately 30% of 553 imatinib-treated patients with CML-CP discontinued imatinib after 4.5 years of follow-up due to insufficient response and adverse events [22]. Studies have compared TKI treatments in respect of achieving complete cytogenetic response (CCyR, Ph-positive meta-phases 0%; BCR-ABL1 transcripts [IS] ≤ 1% at 12 months or later) and significant survival benefit has been associated with CCyR for up to 12 months. Therefore, the primary endpoint of TKI therapy used in CML patients should be to achieve CCyR. In addition, achieving Major Molecular response (MMR) by reaching the target of [IS] 0.1% during treatment increases incident-free survival rates and provides longer CCyR times. In patients with loss of response during treatment, BCR-ABL [IS] >10% after 6 months of treatment or not reaching the CCyR target in 12 months, switching the TKI therapy should be considered [23-25]. In the current study, at 12 months after imatinib treatment, 16 patients

achieved major molecular response (BCR ABL <0.1).

Imatinib was discontinued in 19 patients because of insufficient response to TKI treatment during follow-up and in 10 patients for other reasons, and second generation treatments were then started. Similar to the literature, in 49% of patients first-line TKI treatment was terminated at the end of 12 months and second generation TKI treatment was started [26]. It was observed that dasatinib was preferred in 14 (46.7%) patients and nilotinib was preferred in 15 patients (50%) as a 2nd generation TKI. Bosutinib was not widely used as 2nd generation TKI because of national health insurance protocol issues. Most patients are followed in the CP (85% to 95%) if they are followed-up appropriately and in a timely manner, but if poorly controlled, CML can transform into accelerated or blastic phases very quickly [27]. CML-BP patients have a poor prognosis. It is considered to be the most resistant acute leukemia and objective responses are seen in 20% of patients, with a median survival of 2–5 months [28]. In the current study, despite the use of three different TKIs and strict BCR-ABL [IS] control, 2 patients transformed to blastic phase (AML) and died in less than 1 year.

Nevertheless, TKI discontinuation trials are ongoing worldwide and promising results have started to emerge. Of the current study patients, two were included in the imatinib cessation trial at another center in Turkey. One of these patients remains in treatment-free follow up after 3 years. The other patient had molecular relapse after 1 year without imatinib, and so it was re-started. The patient achieved MMR again and is still being followed up without any complications.

Limitations of this study were the retrospective design and the relatively small study group. With a longer total follow-up period for CML, survival rates after TKI treatment may have been seen to be similar to those of the normal population. There is a need for larger prospective studies to make more detailed analyses.

In conclusion, as imatinib and other next generation TKIs have become widely used in CML patients, survival rates have recently increased, and even become similar to those of healthy subjects. The results of the current study showed that the treatment options, response rates and side-effects were all comparable to the results of other real-world studies. Clinicians should focus on how to obtain the optimal response to drugs and the management of side-effects. Larger patient-based studies are needed to cover the course of the disease and to better manage these patients.

REFERENCES

1. Hochhaus, A., Kantarjian HM, Baccarani M, et al., Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. Blood, 2007. 109: 2303-2309.

2. Faderl, S., Talpaz M, Estrov Z, et al., The biology of chronic myeloid leukemia. New England Journal of Medicine, 1999. 341: 164-172.

3. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. American Journal of Hematology, 2018. 93: 442-459.

4. Hehlmann, R., Innovation in hematology. Perspectives: CML 2016. Haematologica, 2016. 101: 657.

5. Silver RT, Woolf SH, Hehlmann R, et al. An Evidence-Based Analysis of the Effect of Busulfan, Hydroxyurea, Interferon, and Allogeneic Bone Marrow Transplantation in Treating the Chronic

Phase of Chronic Myeloid Leukemia: Developed for the American Society of Hematology: Presented in part at the Education Session of the American Society of Hematology, Blood. 1999. 94: 1517-1536.
6. Martins JRB, Moraes LN, Cury SS, et al. Comparison of microRNA Expression Profile in Chronic Myeloid Leukemia Patients Newly Diagnosed and Treated by Allogeneic Hematopoietic Stem Cell Transplantation. Frontiers in oncology, 2020. 10: 1544.
7. Deininger MW, Shah NP, Altman JK, et al. Chronic Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network, 2020. 18: 1385-1415.
8. Saussele S, Krauss MP, Hehlmann R, et al. Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML study IV. Blood, 2015. 126: 42-49.
9. 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. New England Journal of Medicine, 2003. 348: 994-1004.
10. Giles F, Coutre PD, Pinilla-Ibarz J, et al., Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. Leukemia, 2013. 27: 107-112.
11. Shah NP, Rousselot P, Schiffer C, et al. Dasatinib in imatinib-resistant or-intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. American Journal of Hematology, 2016. 91: 869-874.
12. Brümmendorf TH, Second-Line Bosutinib in Patients with Chronic Phase Chronic Myeloid Leukemia (CP CML) Resistant or Intolerant to Prior Imatinib: An 8-Year Update. Blood, 2017. 130(Supplement 1): 900-900.
13. Cortes JE, Kim DW, Pinilla-Ibarz, et al, Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: final 5-year results of the phase 2 PACE trial. Blood, 2018. 132: 393-404.
14. Cortes JE, Talpaz M, O'Brien S, et al, Staging of chronic myeloid leukemia in the imatinib era: an evaluation of the World Health Organization proposal. Cancer. 2006. 106: 1306-1315.
15. Society, A.C., Cancer facts & figures 2014. 2014: American Cancer Society.
16. Huang X, Cortes J, Kantarjian H, Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer, 2012. 118: 3123-3127.
17. Deininger M. 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. 2009, American Society of Hematology.
18. Şahin F, Saydam G, Cömert M, et al., Turkish chronic myeloid leukemia study: retrospective sectional analysis of CML patients. Turkish Journal of Hematology, 2013. 30: 351.
19. Rohrbacher M. Clinical Trials Underestimate Age of Chronic Myeloid Leukemia (CML) Patients: Epidemiological Study in a Representative Area in Germany. 2007, American Society of Hematology.
20. Zeidan AM, Boddu PC, Patnaik MM, et al. Special considerations in the management of adult patients with acute leukaemias and myeloid neoplasms in the COVID-19 era: recommendations from a panel of international experts. The Lancet Haematology, 2020; 7: e601-e612.
21. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. New England Journal of Medicine, 2006. 355: 2408-2417.
22. Druker B. Long-term benefits of imatinib (IM) for patients newly diagnosed with chronic myelogenous leukemia in chronic phase (CML-CP): the 5-year update from the IRIS study. Journal of Clinical Oncology, 2006. 24(18_suppl): 6506-6506.
23. Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. Journal of clinical oncology, 2010. 28: 2381.
24. Darkow T, Henk HJ, Thomas SK, et al. Treatment inter-ruptions and non-adherence with imatinib and associated healthcare costs. Pharmaco-economics, 2007. 25: 481-496.

25. Noens L, Lierde MA, Bock R, et al., Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. Blood, 2009; 113: 5401-5411.
26. Hochhaus A, Larson RA, Guilhot F, et al., Long-term outcomes of imatinib treatment for chronic myeloid leukemia. New England Journal of Medicine, 2017. 376: 917-927.
27. Reksodiputro AH, Syafei S, Prayago N, et al. Clinical characteristics and hematologic responses to Imatinib in patients with chronic phase myeloid leukemia (CML) at Cipto Mangunkusumo Hospital. Acta Med Indones, 2010. 42: 2-5.
28. Sacchi S, Kantarjian HM, O'Brien, et al., Chronic myelogenous leukemia in nonlymphoid blastic phase: analysis of the results of first salvage therapy with three different treatment approaches for 162 patients. Cancer: 1999. 86: 2632-2641.

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