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REVIEW

Chronic Myeloid Leukemia – A Review of Current Status

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Chronic myeloid leukemia (CML) is a myeloproliferative disorder in which there is a neoplastic proliferation of mature granulocytes. The cancer results from a reciprocal translocation of the breakpoint cluster region (BCR) on chromosome 22 and the ABL1 gene region on chromosome 9 - t (9;22). The result is an abnormal fusion gene on chromosome 22 known as the Philadelphia chromosome. It represents 15% to 20% of all leukemias in the United States with an estimated incidence rate of 1 to 2 cases per 100,000. About 50% of affected individuals are asymptomatic.

Diagnosis depends on demonstrating the presence of the Philadelphia chromosome. CML occurs in 3 phases. The most common is the chronic phase characterized by an indolent course and <15% blast cells in the myeloid space. The remaining advanced phases are the accelerated (15%-30% blasts) and the blast phase (>30% blasts). Without treatment, progression is slow but relentless to the advanced stages and occurs over 3 to 5 years. Survival is markedly reduced once these latter stages are reached. The recognition that the BCR-ABL1 fusion gene was a key driver of the disease process led to the development of tyrosine kinase inhibitor (TKI) drugs that targeted the genetic basis for the cancer. The first of these was imatinib, which was released in 2001. Since then both second and third generations of the drug class have been approved. These medications have been demonstrated to reduce the ratio of abnormal to normal BCR:ABL1 transcripts. They are most effective if used in the chronic phase. The degree of this molecular response has been demonstrated to correlate with limitation of progression of disease and improvement, often marked, of survival. Most individuals who respond well require lifelong use of the medication. However, a subset of the responders may achieve treatment-free remission (TFR) without ongoing therapy. For those individuals who are in the advanced state of the disease, do not respond to the TKI drugs or cannot tolerate them, allogeneic hematopoietic stem cell transplantation (SCT) is an alternative therapy that can achieve long-term survival in some cases.

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Chronic myeloid leukemia (CML) is a myeloproliferative disorder in which there is a neoplastic proliferation of mature granulocytes, primarily neutrophils, but may include basophils and eosinophils as well. The cancer results from a reciprocal translocation of the breakpoint cluster region (BCR) on chromosome 22 and the ABL1 gene region on chromosome 9 – t (9;22). The result of the translocation is an abnormal fusion gene BCR-ABL1 on chromosome 22, designated the Philadelphia chromosome. This modified gene leads

to the abnormal BCR-ABL1 fusion protein that functions as a kinase that phosphorylates tyrosine and leads to abnormal cell division.[1,2]

Globally, the total number of CML cases has increased from approximately 43,000 in 1990 to 66,000 in 2019, although the annual, age-standardized, incidence rate decreased by a little more than 1% per year. The rates are greatest in the regions with the highest sociodemographic index. Because of improved treatment, the estimated age-standardized death rate has decreased at a rate of 2.55% per year globally. In the United States, CML represents approximately 15% to 20% of all leukemias. There were an estimated 9280 new cases in 2024 (0.5% of new cancers) and 1280 estimated deaths (0.2% of all cancer deaths). Overall, the incidence rate is 1 to 2 cases per 100,000. More common in men, the ratio of males to females is approximately 1.35. The median age of onset is approximately 57 in Western countries but younger in developing areas.[1–5]

The major risk factors for CML are male sex (as noted above), increasing age and exposure to very high doses of ionizing radiation. There is no known familial or genetic predisposition to the disease.[1,6]

Up to 50% of individuals with CML are asymptomatic and, in those cases, the disease is found incidentally on routine blood tests or physical examination. Symptoms, when they are present, include fatigue, weight loss, abdominal pain and/or fullness, early satiety, excessive sweating, and acute gout. Other, less common symptoms include bleeding, retinal hemorrhage, and gastric ulceration. Physical findings include splenomegaly and, less commonly, hepatomegaly.[1,7]

Several laboratory findings are characteristic of CML. The complete blood count (CBC) typically shows marked leukocytosis with a median white blood cell (WBC) count of 100,000/uL. However, that count can be as high as 1,000,000/uL. The WBCs usually show cells of all types of the granulocytic line. Although the cells appear normal, they typically have a low leukocyte alkaline phosphatase (LAP). An increase in the absolute number of basophils and eosinophils is common. Anemia occurs in about half of patients and the platelet count can be normal or elevated. Examination of the bone marrow shows hyperplasia of the granulocyte series, reduced erythroid precursors and small megakaryocytes.[1]

Confirmation of the diagnosis depends on demonstrating the presence of the Philadelphia chromosome – t (9;22) by one or more genetic testing techniques. Most individuals with CML will have the abnormal chromosome detected on routine cytogenetics. However, about 2%–5% will have variants that require more sensitive testing. The most sensitive test is the reverse transcription polymerase chain reaction (RT-PCR).[1,7]

CML occurs in 3 phases. The most common, representing 85%–95% of all cases, is the chronic phase. This phase tends to be indolent and is characterized by the leukocytosis and bone marrow findings noted earlier. The distinguishing finding for this phase is the presence of a limited number of blast cells (<15% in the marrow space).

After some period, the chronic phase can progress to an advanced form of the illness which is characterized by worsening signs and symptoms and an increase in the number of blast cells. The accelerated phase may be an intermediate step in progression and is associated with 15%–30% blast cells in the marrow. The most advanced form of the disease is the blast phase (BP) that is characterized by 30% blasts or more. Most frequently, in untreated individuals, those using older therapies, or with therapy failure, this progression is gradual and occurs over 3 to 5 years. However, approximately 5%–15% of individuals with newly diagnosed CML will present in the advanced phase. Survival is markedly reduced with progression to the advanced phase.[7–10]

There are several clinical prognostic scoring systems that assess the risk associated

with CML. These scores all use different combinations of clinical factors such as age, cell, blast and platelet numbers and spleen size to place individuals into low, intermediate or high-risk groups. They include the Euro (Hasford) score, the Sokal score and the European Treatment and Outcome Study for CML (EUTOS) Long-Term Survival scoring system (ELTS). Of these, the latter is probably the best because it reflects the use of current therapy.[8,10,11]

The discovery of the BCR-ABL1 fusion tyrosine kinase activity led to the recognition that this kinase activity was the primary driver for the disease progression in CML. This resulted in the development of tyrosine kinase inhibitor (TKI) drugs. The first of these drugs was imatinib (Gleevec, Imkeldi) that was released in 2001. This led to dramatic responses with prevention of progression to advanced stages in many cases and a marked improvement in outcomes compared to traditional standards. However, some individuals either failed to tolerate the drug or developed resistance to its effects.[2,7,8,12]

Subsequently, several second generation TKI drugs have become available. These include dasatinib (Sprycel, Phryago), nilotinib (Tasigna, Danziten) and bosutinib (Bosulif). These drugs produce a more rapid and deeper response than imatinib but have more significant side effects, including pulmonary and cardiovascular issues, depending on the drug used. No studies have shown improved survival with the second generation TKIs. Thus, all 4 of the above noted first and second generation TKI medications are approved for first-line therapy.[2,7,8,12–14]

In the United States, 2 third generation TKI drugs are approved for use in CML in patients with resistance to first or second generation TKIs due to mutations in the kinase domain. These include asciminib (Scemblix) and ponatinib (Inclusig). The latter medication is the only one that is reliably effective for the T3151 mutation.[2,7,8,11,12]

All the above drugs may be used in chronic as well as advanced phases of CML. However, they are less effective in the latter group.[2,8]

Monitoring the response to therapy is mandatory during treatment with the TKI drugs. At minimum one would want to see a WBC count less than 10,000/uL, no immature cells, less than 5% basophils and a normal platelet count with an absence of Philadelphia chromosome positive cells on cytogenetic analysis.[2,7,8,12]

However, the gold standard for assessing response and prognosis is evaluating the ratio of abnormal fused BCR:ABL1 transcripts to ABL1 transcripts using the International Scale as standardization. Ideally there would be major molecular response (MMR) or MR 3, a 3-log reduction of the baseline ratio of fused to normal ABL1 (0.1% of baseline). Additional levels of reduction are MR 4 (0.01%), MR 4.5 (0.0032%), MR 5 (0.001%) and a complete molecular response (CMR) or an absence of detectable abnormal transcripts. The prognosis improves with the degree of molecular response, the rapidity which it occurs and durability over time. Ideally, one would like to see a deep molecular response or DMR (variously described as MR 4 or MR 4.5 or better) that occurs within 12 months of starting therapy and that persists for at least 2 years. However, the cumulative percentage of individuals who continue to attain this level of response usually continues to increase over time, up to 15 years after onset of therapy in one study.[2,7,8,12,15–17]

The initial goal for treatment with the TKI drugs was to prolong survival from the historical level of 3 to 5 years with traditional therapy. Most patients need to take the medications on a lifelong basis. However, with the recognition that long-term remission was possible with the kinase inhibitors, the goal has shifted to achieving treatment free remission (TFR), which represents long-term remission even after therapy is stopped. To qualify for such an approach, an individual must have reliably taken a TKI drug for 3 years, achieved a DMR that is durable for at least 2 years and be compliant with regular follow

up. Of those who discontinue the medication up to about 40%–50% will achieve a long-term TFR. Most relapses occur in the first 6 months, but about 15% will occur after 2 years. Since it is questionable, even with a TFR, whether the abnormal genetic fusion can be completely eradicated, lifelong monitoring is recommended. Fortunately, restarting the TKI medication after recurrence leads to a response comparable to the one initially achieved in most cases.[2,7,8,18–20]

For those individuals with very high white blood cell counts causing symptoms, resistance to or intolerance of or inability to take the TKI drugs, several alternative approaches are available. Hydroxyurea may be used to acutely lower the WBC count either while awaiting final diagnosis, in conjunction with a TKI drug or during progression to an advanced stage. Interferon, once a mainstay drug for treatment of CML may be used in women who are pregnant or wish to get pregnant since the TKI drugs are contraindicated during pregnancy, especially the first trimester. Traditional chemotherapy is largely reserved for use as palliative treatment for those individuals who have advanced or end-stage disease and who are not candidates for allogeneic hematopoietic stem cell transplantation.[2,7,8,12,21]

Allogeneic stem cell transplantation is a potentially curative therapy for CML. However, it has significant side effects, is very expensive and requirements for the procedure limit the number of individuals who will quality to receive it. Thus, it generally is reserved for those patients who fail or are intolerant of TKI therapy or have presented in or progressed to advanced disease. In the case of patients who enter the blast phase, outcomes are better if they can be returned to the chronic phase before the transplant.[2,7,8,12,21]

Prior to the development of the tyrosine kinase inhibitor drugs survival with CML was poor. Median overall survival was 5 to 7 years with generally relentless progression from the chronic phase to the blast phase over that time. Five-year survival was approximately 40% for individuals aged 20–44 and 20% for those over age 65. With the advent of TKI therapy in 2001, survival has improved dramatically as demonstrated in many studies. This includes data from the US and other countries. Unfortunately, much of this data reviews survival on the total population with CML and does not differentiate survival by the degree of molecular response to therapy.[1,17,22–28]

Considering the importance of molecular response with TKI therapy, only a limited number of papers report survival results in association with the degree of response achieved in the chronic phase of the disease. The best of these articles is by Sasaki et al from the Texas MD Anderson Cancer Center. This group looked at relative survival by the best molecular response achieved at 12 months after starting therapy in patients enrolled in 1 of 6 research studies. The survival was compared to that of the US general population matched for age, gender, race and year of diagnosis. The 10-year absolute overall survival for those individuals achieving a complete cytogenic response (CCyR), major molecular response (MMR or MR 3), MR 4.5 and complete molecular response (CMR) was 83.5%, 87.1%, 89.0%, 88.5% and 91.7%, respectively. The corresponding relative survival compared to the population was 88.3%, 92.1%, 94.1%, 93.9% and 97.3%. Once achieving one of the above levels of response the probability of surviving an additional year remained constant, above 95%.[29,30]

While no other papers show survival data to a comparable level of detail, several show similar survival levels for CCyR, MMR, MR 4 and MR 4.5. Survival is better the earlier in the treatment course the best level of molecular response is achieved.[16,31,32]

Younger individuals, those between the ages of approximately 18 and 40 consistently are shown to have higher levels of adverse prognostic factors such as increased spleen size, higher WBC and blast counts and lower hemoglobin levels. Although there is some variance in different papers, most studies

show that the molecular response to TKI treatment is similar in younger ages to that in older patients. In general, the relative risk of overall mortality risk in the younger individuals is about three times greater than that for middle-aged and older patients.[33–37]

Multiple papers assert that the life expectancy with CML is now normal or near normal relative to the general population. However, the above noted relative survivals would not support this claim. This would especially not be accurate for the life expectancy of a standard life insurance cohort whose LE is longer than that of the general population.[38–40]

In contrast to the good survival achievable with TKI use in the chronic phase, the survival in the accelerated and blast phases remains poor.[41,42]

As noted above, allogeneic hematopoietic cell transplantation (SCT) is now largely reserved as a secondary treatment for individuals who cannot tolerate the TKI drugs, fail to respond to them, have a T3151 mutation that does not respond to ponatinib, who present in the advanced phase or who present in the blast phase but who are able to be returned to the chronic phase. The response to SCT in the first chronic phase is excellent with the achievement of a 2 to 5-year remission without relapse, and results in only a mildly increased relative risk for overall mortality when compared to the population. The survival is not as good if the patient presented in the accelerated or blast phase and was converted to the chronic phase (secondary chronic phase). The outcomes remain poor if a second chronic phase cannot be achieved. Severe and persistent graft vs host disease is an adverse prognostic sign. Prior exposure to TKI drugs does not affect outcomes.[43–51]

Atypical CML is a rare condition with about 1 to 2 episodes per 100 cases of typical CML. It tends to occur in older individuals and is characterized by being Philadelphia chromosome negative and having proliferation of dysplastic granulocytes with other, but not characteristic or diagnostic, cytogenetic anomalies. The only consistently effective therapy is stem cell transplantation. However, because of the older age of onset many patients do not qualify for that treatment. Overall, the prognosis is poor with survival less than 2 years in those individuals who do not achieve a complete cytogenic response with transplantation.[52]

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