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# Answers for the CME: Chronic myeloid leukaemia (CML)

**Q 1** – F, T, F, T, F

**Discussion (MCQ points are highlighted in bold)**

## What is the molecular basis of CML?

Chronic myeloid leukaemia (chronic granulocytic leukaemia) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia (Ph) chromosome. The Ph chromosome was first linked to CML in 1960 by Nowell and Hungerford in Philadelphia. Rowley in 1973 showed this to be a result of a **reciprocal translocation between the long arms of chromosome 9 and 22.** This event, now denoted as t(9;22)(q34;q11), is known to fuse the *BCR* (breakpoint cluster region) and *ABL1* genes together. The resulting ***BCR-ABL1* fusion gene encodes a constitutively active tyrosine kinase** that is central to the pathogenesis of CML.

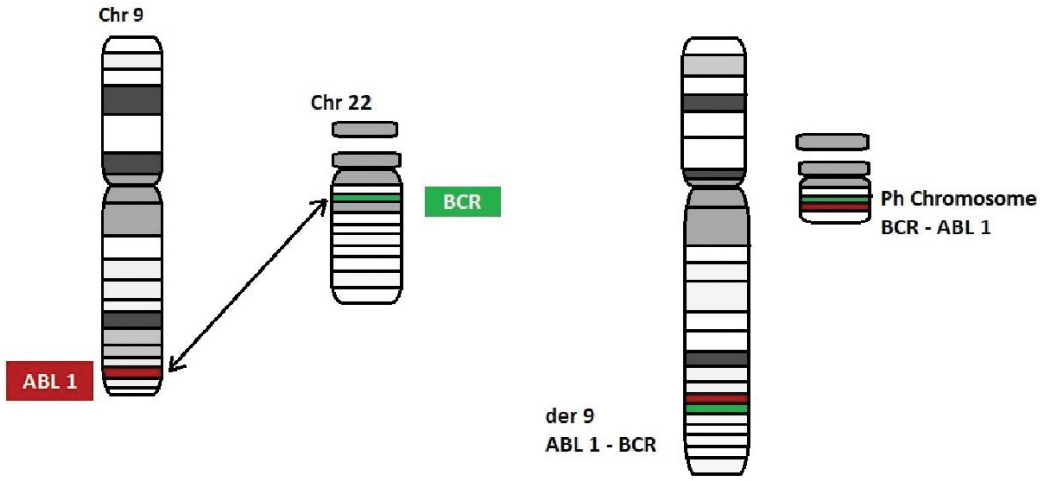



**Figure 1. The t(9;22) translocation leads to juxtaposition of genetic material from chromosomes 9 and 22, with formation of two fusion genes *BCR–ABL1* and *ABL1–BCR*, the former being crucial to the pathogenesis of CML[1].**

At diagnosis, 90-95% of cases of CML have this characteristic translocation. The remaining cases, ~5-10% of patients, have either variant translocations that involve a third or even a fourth chromosome in addition to chromosome 9 and 22 or a cryptic translocation of 9 and 22. These variants have little or no bearing on clinical outcome.

Progression of the disease is usually associated with clonal evolution; at the time of transformation, 80% of cases demonstrate cytogenetic changes in addition to the Ph chromosome, including an **extra Ph chromosome, isochromosome 17q, and gain of chromosome 8 or 19, the so-called major route cytogenetic lesions.** The presence of any of these abnormalities in the karyotype at the time of initial diagnosis of CML has been reported to be an adverse prognostic finding. Therefore, **cytogenetic analysis by conventional karyotype at diagnosis remains important for prognostication**[1,3].

The breakpoints of the *BCR* and *ABL1* genes occur within the introns of each gene and are unique to each individual. The *ABL1* breakpoint is almost invariably located in the intron between exons 1 and 2. The site of the breakpoint in chromosome 22 (*BCR* gene) may influence the phenotype of the disease. **In CML, the *BCR* breakpoint usually occurs in an intron between exons 13-15. The resulting fusion transcripts are named e13a2 and e14a2 transcripts; both may coexist in one individual due to alternate splicing. These transcripts encode for a 210 kDa protein product (p210)**. A breakpoint immediately downstream of the first BCR exon produces the e1a2 transcript, which encodes the **p190 *BCR-ABL1* protein**. This is more commonly seen in Ph+-ALL and is **infrequent in CML. Rarely, the *BCR* breakpoint occurs between exons 17-20, leading to the larger p230 protein** from the e19a2 transcript, which may be associated with a more prominent neutrophilia and/ or thrombocytosis. Other transcripts such as e6a2, e8a2 and e18a2 are also occasionally reported.

## **Q 2** – F, F, F, T, T

### Discussion (MCQ points are highlighted in bold)

**The natural history of untreated CML before the introduction of targeted tyrosine kinase inhibitors (TKI) was biphasic or triphasic: an initial indolent chronic phase (CP) followed by a blast phase (BP), with or without an intervening accelerated phase (AP)**. With TKI therapy and careful disease monitoring, the incidence of progression to advanced phase disease has decreased, and the 10-year overall survival rate for CML is 80-90%. The designation of AP has thus become less relevant, where resistance stemming from *ABL1* kinase mutations and/or additional cytogenetic abnormalities and the development of BP represent key disease attributes. **Accordingly, AP is omitted in the current classification** in favour of an emphasis on high-risk features associated with CP progression and resistance to TKI. Criteria for BP include:

(1) ≥20% myeloid blasts in the blood or bone marrow or (2) the presence of an extramedullary proliferation of blasts or **(3) the presence of increased lymphoblasts in peripheral blood or bone marrow. The optimal cutoff for lymphoblasts and the significance of low-level B-lymphoblasts remain unclear and require additional studie**s[2].

**Progression of the disease is usually associated with clonal evolution**; at the time of transformation, 80% of cases demonstrate cytogenetic changes in addition to the Ph chromosome.

CML-BP is characterized by rapidly rising blast counts and marrow failure as a result of uninhibited growth of myeloid precursors with absence of maturation or differentiation. **Morphologically, CML-BP is indistinguishable from other cases of acute leukaemia**. In ~70% of cases the blasts are of myeloid lineage by morphology and immunophenotype. Blasts in the remaining 25-30% of cases usually express lymphoid antigens of B lineage, with rare cases of T-lymphoblastic and NK cell transformation.

## **Q 3** – F, F, F, T, F

### Discussion (MCQ points are highlighted in bold)

**Four tyrosine kinase inhibitors (TKIs) – imatinib and the second generation (2G) TKIs bosutinib, dasatinib and nilotinib – are now licensed for use in newly diagnosed patients**. The 2GTKIs have been trialed directly against imatinib in large phase III randomised studies with remarkably similar results to each other. Imatinib has a well-established safety profile as well with no life-threatening long-term side effects. Therefore, for most patients there is no indication to choose 2GTKIs over imatinib. However, there are some patient groups in CP that might benefit from 2GTKIs upfront[3].

1. Patients with high or intermediate ELTS or Sokal scores in whom a reduction in disease progression has been demonstrated with a first-line 2GTKI.
2. Women who wish to have children, where the more rapid molecular response achieved with a 2GTKI is desirable.
3. 'Younger' patients, nominally those under 30s and children who are excellent candidates for stem cell transplantation if the need arises, and in whom concerns have been raised regarding more aggressive disease at presentation.

Here, the patient belongs to low-risk group as per ELTS score (Please refer following formula to calculate the score)

The ELTS score is calculated by the formula[4].

**ELTS score = 0.0025 x (age in completed years/10)$^3$ + 0.0615 x spleen size below costal margin + 0.1052 x blasts in peripheral blood + 0.4104 x (platelet count/1000)$^{-0.5}$**

When choosing your values in order to calculate the ELTS score for your patient, please consider the following:

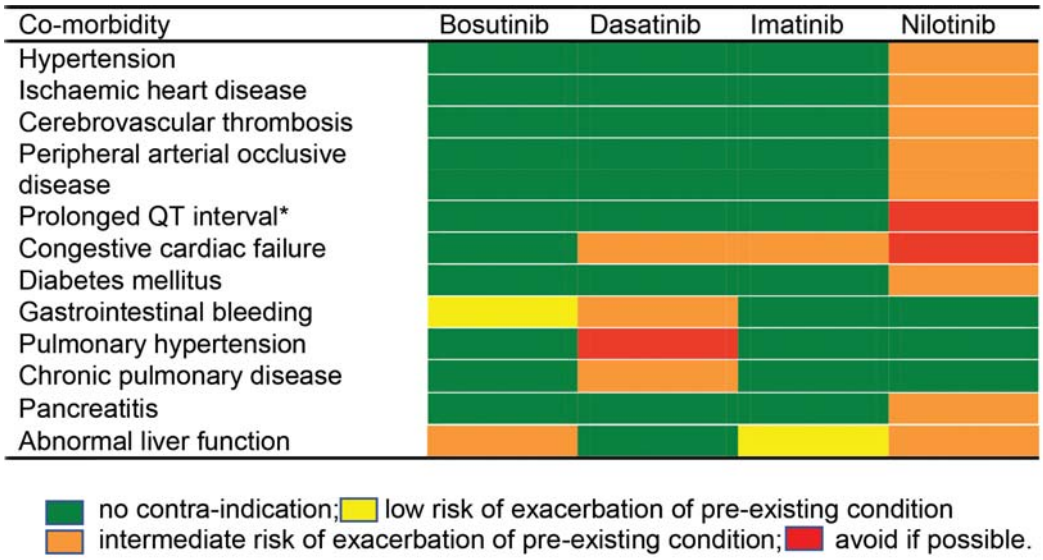
- All variables should be evaluated at diagnosis of the patient.
- Age should be given in completed years. The score was validated for patients above 18 years of age.
- Spleen size should be inserted in cm below the costal margin.
- The percentage of blasts in peripheral blood should be rounded to an integer, e.g. 0, 2 or 7.
- The platelet count should be given in $10^9$/L.

| **Risk group** | **ELTS score** |
|---|---|
| Low-risk group | ≤1.5680 |
| Intermediate-risk group | >1.5680 ≤2.2185 |
| High-risk group | >2.2185 |

(The patient's ELTS score is 1.5571 and therefore he belongs to low-risk group)

Moreover, the early use of a more potent TKI should be balanced against the risk of inducing and/or exacerbating concomitant illnesses. All patients should have a cardiac risk assessment using a cardiovascular disease (CVD) risk assessment algorithm (QRisk3) or equivalent, electrocardiogram (ECG), baseline estimates of lipid profiles, and fasting glucose and/or HbA1c levels. There is potential reactivation of hepatitis viruses with the introduction of TKIs, therefore, all patients should have hepatitis B and C serology assessments prior to treatment.

Guidelines for first-line TKI choice by pre-exiting medical condition (adapted from Michael Deininger, personal communication)[3]




*Some evidence that all 2GTKI prolong QT.

*Imatinib has been associated with the development of gastric antral vascular ectasia (GAVE).

**Imatinib is recommended as a first line TKI treatment for this patient considering the above-mentioned reasons.**

## References

1. Postgraduate Haematology, Seventh Edition. Edited by A Victor Hoffbrand, Douglas R Higgs, David M Keeling and Atul B Mehta.
2. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms; Leukaemia; Joseph D. Khoury; Eric Solary, Oussama et al. 2022.
3. A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia; *British Journal of Haematology* 2020; 191: 171-93.
4. The EUTOS long-term survival (ELTS) score- ELN/ Leukaemia/ CML/ ELTS- score.