BLASTIC CRISIS (BC) OF CHRONIC MYELOID LEUKEMIA

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CML is distinguished by the reciprocal translocation (9;22). The hybrid gene constituted on chromosome 22 (named Philadelphia chromosome-Ph) produces the oncoprotein p^{210} (BCR-ABL1), a tyrosin kinase constitutively activated, expressed in the hematopoietic progenitors, which provokes the apparition and the progression of the disease and determines the response to the monotherapy with specific inhibitors (TKIs).

The introduction of Imatinib and of the 2nd generation TKIs (Dasatinib, Nilotini) as 1st intention therapy has changed dramatically the evolution. Patients who attain the complete cytogenetic response (CCyR) or the major or even the complete molecular response (MMR or CMR, respectively) have a low risk for relapse or progression to BC. The median survival in chronic phase is estimated to 20-25 years. The progression to BC was reduced at 1 – 1,5 % per year in comparison with the pre-Imatinib era (> 20% per year). The median survival in BC is of 7 – 11 mo after Imatinib but only 3-4 mo at patients not treated with TKIs.

The definition of BC used by ELN and other clinical trials is ≥ 30% blast cells in the peripheral blood and bone marrow and the presence of extramedullary infiltrates with blast cells. WHO proposed in 2008 new criteria for BC : ≥ 20% blast cells in the peripheral blood and bone marrow ± clusters of blasts on the medullary sections.

The phenotype of BC may be myeloid (2/3 of cases) or lymphois (1/3 of cases). Rare cases with undifferentiated phenotype or with the aspect of "mixt" leukemia were signaled. BC looks like with AMLs or ALLs but the response to the chemotherapy is different from "de nov" Als.

The progression to BC is the result of the activity of the BCR-ABL oncoprotein. The oncoprotein BCR-ABL transforms the hematopoietic stem cells in leukemic stem cells (LSC), able to generate numerous leukemic progenitor cells (LPC), as coumon leukemic myeloid progenitors (CLMP) and granulo-macrophagic leukemic progenitors (G-MLP). In the chronic phase these LPCs are devoided of the capacity of selfrenewal but can to differentiate in mature cells. In BC the CLMP and the G-MLP gain the capacity of self renewal and begin "stem cells initiators of leukemia". The CML is derived from the stem cells but is conducted by the progenitor cells.

The progression to BC is characterized by the increase of the activity of the BCR-ABL1. This reduces the genomic stability and conducts to the

acquisition of new molecular and chromosomial abnormalities, including punctiform mutations in the tyrosine kinasic domain of the BCR-ABL1. The mutations are the result of the damages of the DNA or of the disregulations of the DNA repair produced by the oxygen reactive species (ROS). They can affect the LSCs or the PLCs and lead to the appearance of clones of LPCs resistant to TKIs or to clones of BC (after accumulation of additional abnormalities). The most frequent abnormal cytogenetic abnormalities (ACA) which are relevant for BC are produced by the "major way" (+8, +19, isochromosome 17q, 2Ph) or, rarely, by the "minor way" (-Y, chr.3 abnormalities).

At the molecular level the most frequent mutations (except those of the TK domain) are in the myeloid BC those of the tumor suppressor gene p53 (20-30% of cases) or of transcription factor RUNX1 gene (38% of cases) and in the lymphoid BC the deletion of IZKF1 gene (which codes the protein IKAROS)(55% of cases), mutations at the CDKN2A/B (50% of cases), deletions of the retinoblastoma suppressor protein. The growth of the BCR-ABL level results in the constitutive activation of a lot of factors (mitogenic, antiapoptotic and antidiferentiation) together with the inhibition of the keys regulators of the cellular processes (p53, C/EBPa, PP2A). A six gene signature (NOB1, DDX47, IGSF2, LTB4R, SCARB1, SLC25A3) can differentiate the early from the late phase of the CML chronic phase, the chronic phase from the accelerated phase and the chronic phase from the BC. The basic principle of the treatment is the deep and rapid reduction of the BCR-ABL1 positive cells. In present it is not realizable the elimination of the "dormant" leukemic CD34+ stem cells.

The management of BC is influenced by the previous treatments and the morphologic type (myeloid or lymphoid) of the leukemia. If the pacient received previously IFN or HUR the indication is a TKI (Imatinib 600-800 mg/day or Dasatinib 140 mg/day, or Nilotinib 400 mg x 2/day). The best result is to obtain a return in chronic phase or a complete remission. An allo-HSCT must be planned. If the BC is not muzzled with the 1st line Imatinib in high doses, the following movement is to pass to a 2nd generation TKI ± chemotherapy followed by the allo-HSCT. The TKI must be choosed after the mutation profile: the Nilotinib if exists the V299L, or T315A, or F317L/V/C; Dasatinib if exists the mutations Y253H, E255K/V or F359V/C/I. For the T315I the indication would be an investigational agent: the Ponatinib. After the failure of TKIs remains the conventional chemotherapy of ALs: anthracyclins plus cytosinarabinoside in AML-BCs, VCR plus Prednison + Dasatinib in ALL-BCs. If a new chronic phase or complete remission in obtained the allo-HSCT is the nest indication if the patient is eligible.

A lot of investigational studies are now in observation : a) **3d generation TKI**: ponatinib – pan BCR-ABL including T315I; DCC-2036: ABL switch pocket; b) **activators of PP2A** : Fingolimod or FTY720; OP449 – SET antagonist; c) **agents target self – renewal of LSC**: ciclopamina : antagonists of transmembrane protein smoothened; HIF1 inhibitor; SAR503 – JAK2 inhibitor; BCL6 + TKI; IL1RAP antibodies; d) **inductors of apoptosis**: ABT737 – BCL2 inhibitor; triptolid; Dual-kinase inhibitor On044580. Peshaps the best treatment of the BC is its prevention by a rigorous and precoce reduction of the BCR-ABL1 or even its elimination. This desideratum can be a hope now.