The prognosis of blast crisis in chronic myelogenous leukemia (BC-CML) is not promising, regardless of the therapy given, and has an expected median survival of 3 to 4 months when the blasts have a myeloid phenotype and 6 to 8 months in lymphoid BC. Indeed, for many groups it is reasonable to treat these patients with supportive care only, particularly those with myeloid BC. Although complete hematological remission in CML after myeloid BC can be obtained in 20% to 60% of the cases, whether these patients also achieve a complete cytogenetic response or not has not been clarified, since chromosomal analysis has been performed only in a few cases. To the best of our knowledge, the cases reported here lack information about the state of the \textit{bcr-abl} fusion gene assessed either by FISH or by RT-PCR analysis.

We report a case of myeloid CML-BC treated with carboplatin and ARA-C in which a complete cytogenetic response was demonstrated, using both conventional cytogenetic and fluorescence in situ hybridization analysis (FISH), although PCR analysis revealed the persistence of minimal residual disease.

**Case report**

A 31-year-old man was diagnosed with CML Ph+ in November of 1994. Peripheral blood count showed: WBC 125×10^9/L (5 lymphocytes; 5 monocytes; 60 neutrophils; 14 myelocytes; 4 metamyelocytes; 8 basophils; 4 eosinophils); Hb 10.8 g/dL; platelets 90×10^9/L. Treatment with hydroxyurea and interferon was immediately initiated, but in January of 1995 the patient suffered a blast crisis with spontaneous spleen rupture and a WBC count of 126×10^9/µL (blasts: 85%). A bone marrow aspirate showed 69% of peroxidase positive myeloblasts which immunophenotyping showed to be CD34+CD33+HLA-DR+. Cytogenetic studies showed 46, XY, t(9;22)(q34;q11)[4]/46, XY, del(7)(q21), t(9;22)(q34;q11)[6]/47,XY,del(7)(q21),+8, t(9,22)(q11;q21)[8].

Treatment with carboplatin (300 mg/m^2/24 hours by continuous infusion days 1 to 5) and ARA-C (500 mg/m^2/24 hours by continuous infusion days 1 to 3) was begun. After one cycle, the bone marrow was in morphological complete remission and cytogenetic analysis showed a normal karyotype (46, XY) in the 40 mitoses analyzed. Evaluation of the \textit{bcr-abl} fusion gene by FISH analysis showed normal hybridization signals without the co-existence of fused signals. By contrast, PCR analysis, using an RT-PCR assay, revealed the persistence of residual \textit{bcr-abl} cells. The patient received a second course of the same chemotherapy, and in addition, G-CSF and peripheral blood progenitor cells (PBPC) were harvested. Upon recovery from aplasia, he received a transplant in May of 1995. A cytogenetic assay in the infused product could not be performed due to the absence of mytosis, but FISH study showed less than 2% of cells positive for \textit{bcr-abl} translocation and persisting disease.

We report on a patient diagnosed with myeloid BC-CML in which a complete cytogenetic remission confirmed by FISH assay was obtained after therapy with carboplatin-ARA-C. However, RT-PCR analysis showed persistence of the p210 \textit{bcr-abl} translocation. Accordingly, the level of residual malignant cells should be between 10^{-2} and 10^{-4}. Autologous stem cell transplantation was performed, but relapse occurred 11 months after blast crisis. This case supports the effectiveness of a carboplatin-ARA-C protocol in BC-CML in order to induce cytogenetic remissions.

**Key words:** blast crisis, chronic myeloid leukemia, carboplatin-ARA-C, complete cytogenetic remission
Carboplatin and Ara-C in CML

(normal upper limit 5%). The sequential immuno-phenotype, cytogenetic and FISH analyses were carried out showing a normal karyotype after autologous transplantation. Molecular studies were also performed in the same samples using a RT-PCR assay which was positive for the p210 bcr-abl translocation.8 The patient remained in hematological and cytogenetic remission until December of 1995, when a second myeloid blast crisis was detected. Cytogenetic studies showed: 46, XY, [1]/46, XY, t(9,22) (q34;q11) [4]/46, XY, del (7)(q21), t(9,22)(q34;q11)[13]. Reinduction with the same chemotherapy used at the first BC was attempted but the patient suffered a pulmonary infection and died in February of 1996.

Discussion:

Although patients with myeloid BC of CML usually display a very poor prognosis, partial or complete hematological responses can be obtained.9 However, the quality of these responses has not been analyzed using sensitive approaches for detection of minimal residual disease. Since CML has a specific leukemic marker (bcr-abl fusion gene), it can be used for monitoring the efficacy of treatment either by FISH or RT-PCR analysis.

Among the different protocols5,10 used for remission induction in patients with CML-BC, the combination of carboplatin-ARA-C infusion has led to surprisingly good results in a pilot study.5 In our patient, this protocol proved to be effective for the achievement of hematological remission. Moreover, both conventional cytogenetics and FISH analysis confirmed the existence of a cytogenetic remission. However, using a more sensitive approach such as RT-PCR, residual bcr-abl leukemic cells were detected. In our hands, the sensitivity of RT-PCR goes down as far as 10^2 (corresponding to a tumor load of 10^3 malignant cells) while the FISH sensitivity ranges between 1 to 3×10^{-2} (corresponding to 10^{10} residual tumor cells); therefore, it can be assumed that in this patient residual leukemic cells remained between 10^2 and 10^3. In order to eliminate the potential residual disease and consolidate remission, we decided to perform an autologous transplant since the patient had no HLA identical sibling. However, this approach proved to be ineffective because relapse occurred 7 months after the transplant. Consequently, other alternatives must be sought out.

The present case shows that carboplatin-ARA-C is able to induce cytogenetic remission in patients with CML-BC, allowing the collection of Ph negative progenitor cells for an autologous transplantation.

References