# A Multicellular Basis for the Origination of Blast Crisis in Chronic Myeloid Leukemia

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Among radiation-induced cancers, some leukemias, including chronic myeloid leukemia (CML) have especially high excess relative risks. CML, sporadic or radiogenic, is also thought to be comparatively very well understood. Accordingly, CML is considered an important model for assessing radiogenic cancer risk. CML is characterized by a specific chromosome translocation, the BCR-ABL fusion gene, and it has been widely postulated that an advanced stage, CML blast crisis originates mainly via cell-autonomous mechanisms such as secondary mutations or genomic instability. However, there is growing evidence that intercellular interactions can play a critical role in cancer evolution, causing us to ask whether CML blast generation is indeed a unicellular event. We investigate this novel possibility using a quantitative, mechanistic cell population dynamics model. This model used recent data on imatinib-treated CML; it also used earlier clinical data, not previously incorporated into current mathematical CML/imatinib models. With the pre-imatinib data, which include results on many more blast crises, we obtained evidence that the driving mechanism for blast crisis origination is a cooperation between specific cell types. Assuming leukemic-normal interactions resulted in a statistically significant improvement in blast crisis prediction over assuming either cell-autonomous mechanisms or interactions between leukemic cells. This conclusion was robust with regard to changes in the model's adjustable parameters. These results have significant implications for CML blast risk modeling that considers a cell-autonomous mechanism as a basic tenet.