not receive therapy because they controlled the infection spontaneously, and these showed comparable responses in ELISpot and proliferation assays. Thus, the responses seen in these antibody-deficient patients who were IFN-α treated are not substantially different from untreated, spontaneously resolved, antibody-deficient individuals, or other spontaneous resolver cohorts, although a much larger cohort would be needed to assess this definitively.

The role of antibodies in long-term antiviral T-cell memory in humans is not known, although it plays a critical role in murine models. Single-source outbreaks of HCV have been highly informative as to the natural history of HCV infection and long-term outcomes of early treatment. Here, such an outbreak provides a unique insight into the longevity of T-cell responses in the absence of antibodies.

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References


To the editor:

Complete regression of cutaneous lesions of refractory Ph+ ALL after 4 weeks of treatment with BMS-354825

Imatinib (Glivec; Novartis, Basel, Switzerland), specifically inhibiting ABL kinase, has evidenced an important role in chronic myeloid and Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemias (ALLs); however, resistance is increasingly encountered, primarily mediated by mutations within the kinase domain of BCR-ABL that interfere with drug binding.

The second generation of tyrosine kinase inhibitors, which include BMS-354825 (Dasatinib; Bristol Myers Squibb, Princeton, NJ), also target ABL, but they appear able to bind also the majority of mutated forms of the protein.

We present the case of a patient with relapsed/refractory Ph+ ALL with disease at extramedullary (cutaneous) and blood level treated with BMS-354825 who achieved complete response in a very short period of time. This 67-year-old male patient was diagnosed with Ph+ ALL (70% Ph+ metaphases, p190 transcript) CD10/CD19/CD38−, in September 2002. He was treated with...
induction chemotherapy and received prophylactic intrathecal methotrexate, achieving complete remission. In March 2003, he was started on maintenance treatment with 400 mg imatinib per day. In July 2004, he complained of severe headache refractory to nonsteroidal anti-inflammatory drugs; a lumbar puncture demonstrated the presence of CD10/CD19/CD38+ lymphoblastic cells. At this time bone marrow revealed no blasts; karyotype, fluorescence in situ hybridization (FISH) and nested polymerase chain reaction (PCR) results were normal. He was given standard intrathecal treatment without the use of Ommaya reservoir, and imatinib was escalated to 400 mg per day. In October 2004 restaging demonstrated remission on both central nervous system (CNS) and bone marrow; thus, imatinib was reduced to 400 mg per day. In March 2005, the patient lost cytogenetic response and presented with a large, indurated, and ulcerated lesion of the scalp. The cutaneous lesion had developed very quickly (10 days), starting with multiple dermohypodermal reddish and painful nodules that conflated into a plaque, rapidly evolving to a central ulceration. Histologic examination showed a diffuse infiltration of the dermis by monomorphous cells with scanty cytoplasm, irregular round to oval nuclei, finely dispersed chromatin, and indistinct nucleoli. Immunohistochemically, these cells expressed CD79a, CD20, and CD10, and expressed chromatin, and indistinct nucleoli. Immunohistochemically, these cells expressed CD79a, CD20, and CD10, and showed nuclear positivity for TdT (terminal deoxynucleotidyl transferase), which was consistent with cutaneous infiltrate of precursor B lymphoblastic leukemia (Figure 1A). No superinfection on the area was evidenced. High-dose steroids had no effect. He was started on BMS-354825\textsuperscript{7,8} on April 12, 2005, with persistence of the large lesion on the scalp (Figure 1B). On days 8 and 15, the skin lesion was much reduced, with disappearance of the erythema and beginning of the healing of the central ulceration (Figure 1Bii-iii). On May 16, 2005, after 4 weeks of treatment with BMS-354825, we evidenced the total remission of the scalp lesion that was completely healed with a hypopigmented scar (Figure 1Biv), while the restaging demonstrated complete hematologic and cytogentic response.

After 5 months of treatment the patient was doing well and in complete remission with no signs of extramedullary disease in skin or CNS. Previous reports have described chronic-phase CML patients with extramedullary (CNS and skin) blastic infiltrates during imatinib therapy, suggesting an incomplete drug penetration\textsuperscript{9,10} at this site. This report suggests a specific and strong activity of BMS-354825 at the cutaneous level.

To the editor:

Discordant distribution of JAK2V617F mutation in siblings with familial myeloproliferative disorders

The recent identification of a somatically acquired, gain-of-function mutation in Janus kinase-2, JAK2V617F (Tefferi and Gilliland\textsuperscript{1} and references therein) in varying proportions of patients with sporadic polycythemia vera (PV) (virtually 100%), idiopathic myelofibrosis (IMF) (50%), and essential thrombocythemia (ET) (25%-50%), raises 2 possibilities with regards to disease pathogenesis: (1) JAK2V617F is sufficient for disease, and the precise phenotype is determined by interindividual differences in genetic background and/or environmental influences; and (2) JAK2V617F is the second mutation in a 2-“hit” model that confers selective growth advantage. Here, the first mutation, which may be genetically heterogeneous and possibly inherited, is also required for disease development.

The study of familial myeloproliferative diseases (MPDs) provides a unique opportunity to distinguish between the above possibilities. Families in which first-degree relatives develop MPDs that are indistinguishable from sporadic MPDs have been previously described, and suggest an autosomal dominant inheritance with incomplete penetrance, particularly for expression of the full disease phenotype.\textsuperscript{2,3} Notably, a study of 6 families with multiple members with PV revealed clonal hematopoiesis in affected females and erythropoietin-independent erythroid progenitors in healthy family members, thus implicating multiple genetic defects in the early pathogenesis of PV.\textsuperscript{4} Importantly, in this study, linkage analysis suggested that loss of heterozygosity (LOH) of chromosome 9p (where JAK2 is located) is a secondary change and does not target the primary PV locus. In another pedigree with familial PV, where the 2 affected members were linked by an unaffected obligate carrier, all 3 individuals were found to...
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