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Juvenile myelomonocytic leukemia

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Juvenile myelomonocytic leukemia (JMML) is a rare clonal myeloproliferative disorder (MPD) of early childhood [1]. The median age at diagnosis is 2 years [1]. There is a male predominance with a male:female ratio of 2:1. Pallor, fever, infection, skin bleeding and cough are the most common presenting symptoms. Typically, there is marked hepatosplenomegaly. JMML rarely involves the central nervous system.

Laboratory findings

Laboratory findings include leukocytosis, anemia and thrombocytopenia. The median white count is 33×10^9/L [1]. An absolute monocyte count greater than 1×10^9/L is required for the diagnosis [2]. The blast cell percentage in peripheral blood (PB) rarely exceeds 20% and is most often below 2% [1]. Cytogenetic studies of JMML cells show a normal karyotype in 65% of patients, monosomy 7 in 25%, and other abnormalities in 10% [1]. Patients with monosomy 7 present with a normal or moderately elevated HbF. In patients with normal karyotype HbF is often elevated [1].

Aberrant Ras signaling

The Ras signaling transduction pathway is deregulated in JMML. JMML myeloid progenitors are hypersensitive to granulocyte-macrophage colony stimulating factor (GM-CSF) in vitro [3]. This observation is linked to mutations that lead to aberrant Ras signaling. Approximately 35% of the cases harbor somatic mutations in exons 3 or 13 of the PTPN11 gene [4–6]. The PTPN11 gene product, SHP-2, is a non-receptor protein tyrosine phosphatase that relays signals from growth factor receptors to Ras and other signaling molecules [7]. RAS genes encode 21-kDa signal switch molecules that regulate cell fates by cycling between inactive GDP-bound (Ras-GDP) and active GTP-bound (Ras-GTP) conformations. Somatic NRAS or KRAS2 mutations are identified in 15–25% of JMML cases [8,9]. These lesions lead to substitutions at codons G12, G13, or Q61 and impair the intrinsic Ras GTPase and confer resistance to GTPase-activating proteins. In 11% of patients with JMML the clinical diagnosis of neurofibromatosis type 1 (NF1) can be made [10]. However, it has been shown that some infants with JMML carry germ line neurofibromatosis type 1 gene (NF1) mutations although the diagnosis of NF1 had not been made clinically [11]. Neurofibromin, the gene product of the NF1 tumor suppressor gene, negatively regulates Ras by functioning as GTPase activating protein. Thus, loss of neurofibromin leads to aberrant Ras signaling. Indeed, analysis of JMML cells from patients with NF1 showed an elevated percentage of Ras in the active GTP-bound conformation [12]. Taken together, approximately 85% of all patients with JMML carry mutations in PTPN11, RAS, or NF1 (Figure I). Of note, these mutations are largely mutually exclusive suggesting that they disrupt identical pathways in myeloid cells [4,5].

Murine models

Mouse models support the idea that in JMML mutations in NF1, RAS, or PTPN11 are initiating rather than later cooperating events. By generating mice whose hematopoietic system was reconstituted with NF1 deficient hematopoietic stem cells it has been shown that NF1 loss, by itself, is sufficient to produce a JMML-like disorder in mice [13]. In addition, somatic inactivation of NF1 results in a fatal myeloproliferative disease with shift in hematopoiesis from the BM to spleen, an increased number of T-and B-cells and resistance to apoptosis [14]. Similarly, somatic activation of oncogenic Ras in hematopoietic cells initiates a rapidly fatal myelopro-

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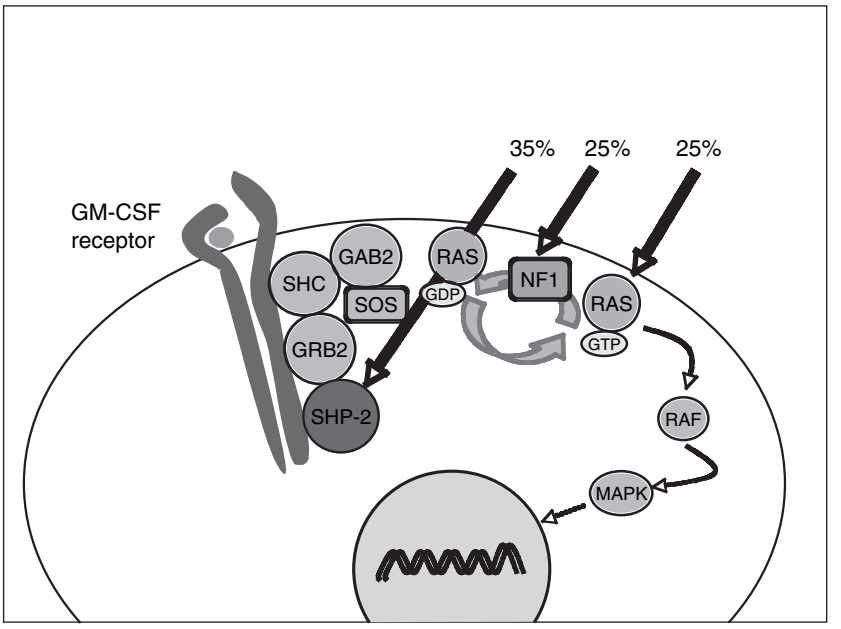

Figure I. Model outlining the roles of SHP-2, RAS, and NF1 in the granulocyte-macrophage colony-stimulating factor (GM-CSF) signal transduction pathway. In juvenile myelomonocytic leukemia (JMML), molecular alterations have been demonstrated in PTPN11 (the gene encoding SHP-2), RAS and NF1 in approximately 35%, 25% and 25% of patients, respectively.

liferative disorder [15]. Finally, in a murine model of Noonan syndrome (see below), mice carrying an activated PTPN11 allele develop a mild myeloproliferative disease [16].

Noonan syndrome and juvenile myelomoncytic leukemia

Noonan syndrome is an autosomal dominant developmental disorder characterized by dysmorphic facial features, growth retardation and variable congenital heart defects. In one half of the cases the disorder is caused by heterozygous germ line PTPN11 mutations [7]. A small number of infants with Noonan syndrome develop a JMML-like disease [17]. In these young children with Noonan syndrome and JMML-like disease, the spontaneous remission of the disorder is well documented [17]. PTPN11 mutations observed in Noonan Syndrome are predicted to have generally mild gain-of-function effects. In contrast, PTPN11 mutations associated with JMML lead to stronger activation of SHP-2. Mutations in patients with Noonan syndrome who develop a JMML-like disease are predicted to have intermediate effects. Consistent with this model, in vitro and in vivo experiments on primary hematopoietic cells and cell lines show that somatic mutants confer more pronounced effects on cell growth than common mutants only found in Noonan syndrome [18,19].

Diagnosis

Diagnostic criteria have been proposed by the International JMML Working Group in 1998 (Table I) [2]. However, molecular studies have greatly facilitated the diagnostic approach and mutational studies have become an important tool in the diagnostic process of JMML. JMML can be mimicked by a variety of infectious agents such as cytomegalovirus, Epstein-Barr virus, human herpes virus 6 and parvovirus B19. Positive results of these viruses do not exclude the diagnosis of JMML.

Natural course if the disease

JMML is a rapidly fatal disorder for most children if left untreated. The median survival time without hematopoietic stem cell transplantation (HSCT) is

Table I. Diagnostic guidelines for juvenile myelomoncytic leukemia (JMML) [adopted from [2]]

I. Suggestive clinical features
Hepatosplenomegaly
Lymphadenopathy
Pallor
Fever
Skin rash
II. Laboratory criteria (all 3 are mandatory)
Absence of Philadelphia chromosome (*BCR/ABL* rearrangement)
Peripheral blood monocyte count $>1 \times 10^9$/L
Blast percentage in BM $<20\%$
III. Criteria for definite diagnosis (at least 2 must be fulfilled)
Hemoglobin F increased for age
Myeloid precursors on peripheral blood smear
White blood count $>10 \times 10^9$/L
Clonal abnormality
Granulocyte-macrophage colony-stimulating factor (GM-CSF) hypersensitivity of myeloid progenitors in vitro

about 1 year [1]. Low platelet count, age above 2 years at diagnosis and high HbF at diagnosis are main predictors of short survival [1]. Blastic transformation is infrequent in JMML. Most untreated patients die from respiratory failure caused by infiltration of the lungs with JMML cells.

Antileukemic therapy

The role of antileukemic therapy prior to HSCT is currently uncertain. The current JMML study of the Children's Oncology Group (COG) prescribes cytoreductive therapy consisting of fludarabine and high-dose cytarabine concomitantly with 13-cis retinoic acid prior to HSCT, while most patients in Europe traditionally receive mercaptopurine or no therapy. Therapeutic strategies targeting individual components of the Ras signaling pathway include the administration of the GM-CSF analog E21R and the farnesyltransferase inhibitor R115777 (Zarnestra®) [20].

Stem cell transplantation

Allogeneic HSCT is currently the only curative treatment for JMML. The analysis of the EWOG-MDS/EBMT trial of 100 patients with JMML transplanted with a preparative regiment of busulfan, cyclophosphamide and melphalan shows a 5-year probability of EFS of 52% [21]. The EFS of patients transplanted from a matched family donor (MFD) and unrelated donor (URD) are not significantly different. In the current EWOG-MDS/EBMT trial, the 5-year cumulative incidence of relapse was 35% [21]. Relapse occurs early, at a median of 2 to 6 months from transplantation [21] and generally within the first year. HSCT shortly after diagnosis is recommended, because younger age at HSCT predicts improved survival [21]. In the prospective HSCT study from EWOG-MDS, multivariate analysis shows age greater than 4 years and female sex predicted poorer outcome [21]. Cytogenetic abnormalities do not confer a worse prognosis [21]. In the current HSCT study of the EWOG-MDS, splenectomy did not improve the survival after HSCT [21].

Relapse

Disease recurrence remains the major cause of treatment failure. Median time from HSCT to relapse is 4–6 months with only few patients relapsing more than 1 year after transplantation [21]. Graft-versus-leukemia (GVL) effect plays an important role in curing children with JMML with HSCT. Re-emerging donor cells and frank hematologic relapse have been successfully eradicated by reduction of ongoing immunosuppressive therapy. Reducing the intensity and duration of graft-versus-host disease (GVHD) prophylaxis may significantly contribute to successful leukemia control. However, donor lymphocyte infusion in JMML relapse has largely been unsuccessful [22]. Serial quantitative chimerism studies can identify patients with increasing mixed chimersim who are at high risk for relapse of JMML. Immediate withdrawal of immunosuppressive therapy is advised in these patients [23]. Despite aggressive re-emergence of the malignant clone and short interval between the first and second HSCT, a substantial proportion of children can be cured after a second HSCT [24].

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