INTRODUCTION

Therapy-related myelodysplastic syndromes (t-MDS) occur in patients exposed to genotoxic chemotherapy, irradiation, or both. At least 20,000 cases of MDS were diagnosed in the U.S. in 2008, of which approximately 10% were therapy-related. Because objective diagnostic criteria for t-MDS are lacking, this likely underestimates the true incidence. Cases are attributed to previous therapy based on circumstantial evidence, including the (1) presence of typical clonal cytogenetic abnormalities, (2) significant exposure to leukemogenic therapy (ie, at least 1 cycle), and (3) sufficient latency from exposure to diagnosis of t-MDS (ie, at least 6 months).

Alkylating agents are the principal cause of t-MDS. The syndrome was first recognized in the treatment of Hodgkin disease (HD), in which a relationship between alkylator dose and risk of t-MDS/acute myelogenous leukemia (AML) was established [1,2]. This thinking has been extrapolated to the autologous stem cell transplantation (SCT) population as a potential explanation for t-MDS rates as high as 10% [3]. There are several sources of bias in these retrospective reports, because SCT recipients often are heavily pretreated and have increased survival after transplantation (and thus have more years “at risk” for t-MDS). Indeed, there is evidence of clonal abnormalities at the time of transplantation in some patients who subsequently develop t-MDS/AML [4,5]. Nevertheless, at least one prospective, randomized trial in patients with follicular lymphoma demonstrated a higher rate of t-MDS/AML in the high-dose chemotherapy arm compared with the conventional-dose chemotherapy arm (7% vs 0%; \( P = .014 \)), suggesting that the transplantation procedure contributes directly to leukemia risk [6]. In most series, higher rates of t-MDS/AML have been reported in patients conditioned with total body irradiation (TBI)-containing regimens [3].

Therapy-related leukemia also can be caused by exposure to topoisomerase II inhibitors. These patients typically present with t-AML without a preceding MDS phase. Because most patients receive combination chemotherapy, it often is impossible to assign blame to a particular agent. Regardless of the cause, t-MDS/AML has an inferior prognosis compared with de novo disease [7]. The only curative option is autologous SCT [8]. In this sense, this disease is unique among hematopoietic malignancies, in that hematopoietic SCT is both an important cause and the only available cure.

GENETICS

Recurring genetic abnormalities in t-MDS have been defined across the full spectrum of analytical platforms from cytogenetics to gene resequencing. Loss of material from chromosomes 5 and/or 7 is detectable in up to 70% of t-MDS/AML patients, often with other abnormalities in a complex karyotype [9]. The same pattern of cytogenetic abnormalities occurs in de novo MDS, but at a much lower frequency [10]. Through the work of many investigators, the minimally deleted regions on chromosomes 5 and 7 have been mapped, and the residual alleles have been examined for loss of heterozygosity. We performed a comprehensive analysis of the minimally deleted region on 5q31.2 using array comparative genomic hybridization, gene resequencing, and expression profiling. All 28 genes in the region on the unaffected chromosome...
were present in germline configuration in this cohort, with no gene consistently silenced [11]. This study and others suggest that multiple genes on 5q31.2 contribute to t-MDS by haploinsufficiency. Similarly, no single culprit has been identified on 7q, raising the possibility that a similar mechanism may apply.

Mutational profiling of individual candidate genes has revealed unique features of t-MDS. Point mutations in TP53, RUNX1, and K/NRAS are more common in t-MDS compared with de novo MDS (approximately 25% vs 10%, 20% vs 10%, and 5%-10% vs 5%, respectively), whereas mutations in FLT3 are relatively underrepresented in t-MDS [12-16]. Ongoing studies using transcriptome, whole exome, and whole genome sequencing approaches will provide an unbiased comparison of the genetic landscape in t-MDS and de novo MDS.

In addition to these somatic changes, there may be a genetic component to t-MDS susceptibility. Rare familial cancer predisposition syndromes provide proof of principle that inherited genetic variants can influence the susceptibility to t-MDS/AML. For example, children with neurofibromatosis-1 (NF1) are at 200- to 500-fold greater risk for developing myeloid malignancies [17], and t-MDS can occur as a second malignancy in adult NF patients exposed to alkylators [18]. In sporadic t-MDS/AML, candidate gene association studies have focused on genes involved in drug detoxification and DNA repair. More than 30 published studies have examined the role of variants in the conjugating enzymes involved in phase II metabolism. A meta-analysis criticized most of these studies for inadequate sample size and population heterogeneity [19]. Associations with the deleted genotypes of the glutathione S-transferases, GSTM1 and GSTT1, are mostly null. Heterozygosity of the codon 105 polymorphism in GSTP1 does appear to increase the risk of t-MDS/AML (odds ratio [OR] = 2.66; 95% confidence interval [CI] = 1.39-5.09) [20]. In phase I metabolism, the poor-metabolizer genotypes of CYP2C19 or CYP2D6 do not appear to be associated with t-MDS/AML risk [21], whereas reduced risk (OR = 0.07) was associated with the variant allele in the 5′ promoter of CYP3A4 [22]. Common polymorphisms in genes involved in the response to drug-induced DNA damage also have been implicated as risk factors for t-MDS/AML. Like changes in genes involved in drug detoxification, the relative risks associated with these variations are small (generally, OR < 2.0). Increased risk of t-MDS/AML has been demonstrated with the Lys751Gln variant of ERCC2 (XPD) [23], a single-nucleotide polymorphism (SNP) in exon 13 of MSH2 [24], and reduced risk associated with Arg399Gln of XRCC1 [25]. Many of these associations have been difficult to replicate, as is often the case in underpowered gene association studies. Sample size is an even greater constraint in genome-wide association studies, although one recent publication reported significantly more SNP associations in t-MDS/AML than would be expected by chance [26].

MODELS

Animal models of t-MDS provide platforms for identifying both recurring mutations relevant for human t-MDS and germline alleles that affect susceptibility. For example, heterozygous Nf1 mutant mice are susceptible to a spectrum of spontaneous and therapy-induced myeloid malignancies that resembles the pattern seen in humans with germline NF1 mutations [27]. To identify novel genes associated with t-MDS susceptibility, we performed a genome-wide screen in mice. We exposed a large panel of inbred strains to the prototypical alkylator N-nitroso-N-ethylurea (ENU). Myeloid malignancies (eg, MDS, AML, granulocytic sarcoma) were induced in a strain-dependent manner, supporting the notion that there is a genetic component to susceptibility [28]. An F2 intercross between susceptible and resistant strains identified loci associated with leukemia-free survival after ENU [29]. Fine-mapping these intervals has identified candidate genes that currently are being tested for their importance in t-MDS/AML susceptibility.

Several other mouse models of human MDS have been generated using transgenic, gene targeting, and retroviral transduction/transplantation approaches [30]. Although these models recapitulate (to varying degrees) the phenotype of human MDS, they are defined by single genetic events and thus do not capture the complexity of t-MDS. Similarly, other animal models of MDS exist [30] that have not yet been exploited to study t-MDS.

BENCH TO BEDSIDE

Ongoing genomic studies in patients and animal models of t-MDS will provide new information that may be translated into strategies for improving the treatment and prevention of t-MDS. Identification of recurring mutations may provide new targets for therapy. Translating knowledge of susceptibility alleles into t-MDS prevention and control strategies may prove more challenging. One approach would be to identify patients with high-risk genotypes and tailor their therapy accordingly. Many caveats apply here; the effect size of the genotype must be relatively large, the prevalence of variant alleles in the population must be relatively high, and equipotent chemotherapy must be available. Providing suboptimal chemotherapy to a relatively large group of patients with potentially curable malignancies to prevent a rare (albeit serious) complication is an unacceptable trade-off. A second strategy would be to offer intensive surveillance for...
t-MDS after alkylator exposure in patients with high genotype-specific relative risk. This effort would be justified only if there was evidence that chemotherapy delays progression from t-MDS to t-AML, or that early transplantation improves overall survival (OS) in t-MDS. A final approach, which is more speculative at this stage, may prove most useful in the long term. It is predicated on understanding the biochemical events relevant for t-MDS initiation. If key regulatory factors can be identified, then it may be possible to perturb these factors during alkylator exposure in such a way as to preserve antitumor efficacy, but reduce hematologic toxicity. These approaches all require additional work in animal models before clinical trials can be-initiated. Because patients undergoing autologous SCT are at high risk, they may be an ideal population to recruit to these trials. A successful outcome will certainly depend on broad support from the transplantation community.

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REFERENCES