

Event Related (Secondary) Myelodysplastic Syndromes (MDS): The impact of Success

John M. Bennett, MD

James P. Wilmot Cancer Center, University of Rochester
Medical Center, Rochester, New York



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In order to understand the pathobiology of event associated MDS one must appreciate what primary or "idiopathic" MDS represent. These are a group of malignant hematopoietic marrow disorders that share an ineffective production of one or more myeloid cell lines (accelerated apoptosis) with a variable percent of leukemic blasts (ranging from <5% to 20%). The net result is a discrepancy between a cellular marrow and peripheral cytopenias (marrow failure). The median age is 70 years and 30% progress to Acute Myeloid Leukemia within 5 years. In the USA approximately 15,000 cases are diagnosed annually.

The vast majority of Event Related MDS are the results of chemotherapy and (or) radiation intervention in patients with a known malignancy that requires treatment. Another cause is the increasing use of immunosuppression in transplantation medicine (alloBMT; cardiac; liver, etc.). Very few proven cases have been associated with environmental toxins. The two major classes of mutagenic agents are alkylators, ionizing radiation and topoisomerase-2 inhibitors. The identification of pharmacogenomic polymorphisms (e.g. NQO1; GSTq 1-null) are an increasing important aspect of exposure reactions.

Alkylating agents are associated with a long latency (4 + years) and a high frequency of chromosomal deletions (-5; -7) whereas Topo-II targeting agents (etoposides, anthracyclines) have a short latency (1 year) and specific chromosomal translocations with t(3;21); t(8;21); t(15;17), inv.16, as well as 11 q 23 rearrangements.

One example of the over expression of methylation of genes involved in marrow regulation of cellular growth is seen in the higher % of p15-ink in secondary AML and the association with 7q- and very short survival. Another example involves the mutation of the AML1 transcription factor (16% in

patients with t-MDS/AML). Further evidence of involvement is noted with complex arrangements with CBF and AMP1.

Secondary AML/MDS represents about 15% of the total number of MDS/AML diagnosed each year. Antecedent malignancies vary with institutional referral patterns but solid tumors (breast, lung) and hematologic malignancy accounts for about 80% of all reported cases.

Overall survival is short, usually <1 year with longer survival for patients with balanced translocations.

A well studied series of over 1,000 patients with NHL exposed to a radionuclide indicates an overall incidence of 2.2%, all exposed to other alkylating agents as well.

In addition a small number of cases of ALL secondary to topo-II inhibitors have been noted often with [t(4;11)] representing about 10% of all of the secondary leukemias reported to date.

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