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[haematologica reports]
2006;2(15):1-2

Secondary leukemias and leukeogenesis

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The last annual combined report from the American Cancer Society, NCI, CDC and NAACCR provided information on cancer rates and trends in United States from 1975 to 2002. This survey showed that among men the incidence rates for all cancer were stable, while among women they increased by 0.3% annually. On the other hand the overall cancer death rates decreased by 1.1% from 1993 through 2002.¹ On this basis, there is a high number of patients surviving at long-term, at risk to develop a secondary acute myeloid leukemia or myelodysplastic syndromes (t-AML/MDS).

Cancer is a multi-factorial disease: genetic factors, by themselves, could explain 5% of all cancer, the remainder can be attributed to environmental carcinogens, tobacco smoke, dietary constituents, pollutants, drugs, radiations, and infectious agents. Radiotherapy and chemotherapy are the most established causes of second malignant neoplasm, and leukemia is the most frequent neoplasm subsequent to chemotherapy and/or radiotherapy. Acute myeloid leukaemia developing after exposure to genotoxic agents has been recognized as a distinctive entity for more than 40 years, and secondary, or therapy-related, t-AML accounts for 10% to 20% of all AML cases.

While radiotherapy and/or chemotherapy are efficacious as anti-cancer agents in a high proportion of patients, only a low number of patients develop a secondary leukemia. Different variables are involved in leukemogenesis. It has been hypothesized that different drug catabolism or different drug membrane transport induce the predisposition to develop leukemia. In addition, differences in DNA damage repair can also explain this phenomenon.

Many attempts have been made to

identify both environmental and genetic predisposing factors to secondary leukemia, but the studies are limited to single centers and to small areas of the continent. Secondary leukemias are frequently excluded from collaborative multicentric trials because of their different behaviour and their response to therapy, different from *de novo* leukemias. The actual incidence of t-AML is not known, and even when they are registered in multicenter trials, data collection is insufficient due to the low absolute number of cases, and also to different collection methods in trials from the same country. Genomic studies are performed by few centers only, and epidemiological studies lose their strength if not complemented by cellular and molecular biology data.

Starting from 1998, and every 4 years, we have organized at the Hematology Institute of the Catholic University in Rome a Congress on Secondary Leukemias, which was attended by many outstanding american and european researchers. This event provides an opportunity to exchange experiences and knowledge with all invited speakers from Europe and United States.

The major points our Symposium on Secondary Leukemias and Leukemogenesis focuses on are:

1) design and implementation of longitudinal clinical and genetic monitoring of high-risk populations (ie, to identify individuals undergoing cytotoxic therapies for primary malignancies, individuals exposed to radiation)

2) identification and application of accurate biomarkers of leukemogenesis, for the purpose of risk prediction and quantification, potentially allowing recognition of patients especially susceptible to the leukemogenic effects of chemotherapy (for genetic or acquired reasons) and allowing their treatment for cancer;

3) identification and characterization of mechanisms of DNA damage and the orderly repair of such damage;

4) dissection of the molecular structure of the induced genetic lesions and identification of the functional consequences of these changes, thereby providing clues into the pathogenesis of secondary AML and potentially serving as a basis for innovative therapeutic interventions.

References

1. Edwards BK, Brown ML, Wingo PA, Howe HL, Ward E, Ries LAG, et al. Annual report to the nation on the status of cancer, 1975-2002, featuring population-based trends in cancer treatment. *J Natl Cancer Inst.* 2005;97:1407-27.