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Secondary or therapy-related MDS and AML and their chromosome aberrations: important to study but difficult to establish causality

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Why it is important to study t-MDS and t-AML

Secondary or therapy-related myelodysplastic syndrome (t-MDS), often leading to overt acute myeloid leukemia (t-AML), is important to study for at least four reasons (Table 1). First, because it has become the most serious and feared long term complication of current cancer chemotherapy. The high risk of t-MDS and t-AML observed in many studies and primarily related to the administration of alkylating agents has, for example in patients with polycythemia vera, displaced these drugs as first line therapy.[1] Furthermore, the risk of t-MDS and t-AML has markedly reduced the administration of alkylating agents to patients with many benign diseases such as rheumatoid arthritis, nephritis and systemic LED, and has even decreased the use of alkylating agents in malignant diseases. As an example, high dose chemotherapy followed by autologous stem cell transplantation is now recommended as first-line therapy for patients with aggressive lymphomas,[2] because, among other reasons, of a particularly high risk of t-MDS and t-AML if the intensive therapy is administered as second- or third-line therapy after multiple courses of chemotherapy with regimens including alkylating agents.[3]

Secondly, in leukemia research t-MDS/t-AML is unique since this disease is caused by well-defined chemical agents or less often irradiation administered in well-controlled doses and at a definite point of time (Table 1). In patients with Hodgkin's disease, as an example, this well-defined exposure has made it possible to demonstrate an increase in the cumulative risk of t-MDS and t-AML directly proportional to the cumulative dose of alkylating agents.[4] The closely studied cellular effects of irradiation and cytostatic agents may lead to further etiological insights.

Thirdly, studies of t-MDS and t-AML may result in an increased understanding of the multistep pathogenesis of leukemic transformation (Table 1). In *de novo* AML information on a preleukemic MDS stage is in most cases lacking, whereas in t-AML such information is most often present, because of a close clinical follow-up after intensive radiotherapy or chemotherapy. In a study of chromosome aberrations this fact has allowed the identification of different leukemogenetic pathways in t-MDS and in t-AML as indicated by significant differences in the cytogenetic characteristics.[5] Further studies along these lines, also of genetic changes unrelated to chromosome aberrations, may result in an increased knowledge of the multistep pathogenesis of leukemia.

Finally, the study of t-MDS and t-AML is important because most cases present chromosome abnormalities reflecting the etiology and the molecular biology of the disease (Table 1). These last aspects have recently been discussed in more detail elsewhere,[6] and will be elaborated further in an accompanying article.[7] In this issue of *Haematologica*, the prognosis and therapy of t-MDS, the most serious long-term complication of current cancer therapy, will also be discussed more extensively.[8]

Reasons for the difficulty of demonstrating causality in t-MDS and t-AML

After the clinical introduction of the alkylating agents it took many years to identify this group of cytostatic drugs as the most important risk factor for the development of t-MDS and t-AML following cancer chemotherapy[9-12] and to demonstrate that high-dose radiotherapy is a much less important risk factor. Likewise, several years passed before the leukemogenic potential of the DNA topoisomerase II inhibitors was realized.[13-16] Whereas deletions of the long arms or loss of whole chromosomes #5 and #7 in t-MDS and t-AML for many years have been associated with previous therapy with alkylating agents,[17] it was only demonstrated recently that t-MDS and t-AML with balanced translocations to chromosome bands 11q23 and 21q22 were significantly associated with previous therapy with DNA topoisomerase II inhibitors.[18,19] Table 2 summarizes some reasons for this delayed recognition and controversy in the assessment of risk factors all relating to basic problems of demonstrating causality in t-MDS and t-AML.

Although 10-20% of cases of newly diagnosed MDS and AML in many centers are now secondary or therapy-related, t-MDS and t-AML is still a relatively infrequent complication of cancer therapy. Furthermore, there is a lack of specific association since leukemias, like other tumors in man, are not homogeneous like many experimental animal tumors. Thus, single cases of t-AML may present almost all cytologic types of leukemia, with many different cytogenetic characteristics related to all types of therapy. Another major problem in the demonstration of causality relates to the fact that many cases of t-MDS and t-AML remain undiagnosed. If an early stage of t-MDS develops a long time

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Table 1. Reasons why it is important to study t-MDS and t-AML.

1. They represent the most serious long-term complication of cancer chemotherapy.
2. They are caused by chemically well-defined agents or irradiation administered in well-defined doses and at a definite time.
3. They are an example of the multistep model for malignant transformation and are often diagnosed at an early stage due to a close clinical follow-up.
4. Most cases present chromosome abnormalities which may reflect the etiology and the molecular biology of the disease.

Table 2. Reasons why it is difficult to demonstrate causality in t-MDS and t-AML.

1. They are a less frequent complication
2. The lack of specific associations
3. They may remain undiagnosed (long latent period, brief survival, metastatic primary tumor, loss of follow-up)
4. In individual cases it may be difficult to distinguish between spontaneous MDS or AML de-novo and directly therapy-induced disease
5. Often complicated therapy for the primary tumor (multi-drug regimens frequently including radiotherapy).
6. Many different chromosome aberrations are observed, but each abnormality is often seen in only a few cases. Confounding factors such as age, race and differences in follow-up.

after therapy in an old, heavily treated patient, possibly in relapse and suffering from dissemination of the primary tumor, diagnostic interventions such as bone marrow aspiration or even blood tests, are often cancelled, or the patient may even be lost to clinical follow-up. For these reasons, we consider t-MDS as the most frequently undiagnosed hematologic malignancy of man.

In individual cases of t-MDS or t-AML it is difficult or impossible to distinguish between spontaneous *de novo* disease and directly therapy-induced cases, and the administration of combined modality therapy and multi-drug combinations further adds to the many problems in demonstrating causality. Finally, many different cytogenetic abnormalities are often observed in only a few patients, for which reason larger series of patients must be studied. Confounding factors such as differences in follow-up, race and most important, age, may, as shown in the accompanying article, cause problems in a study of causality of chromosome aberrations in t-MDS and t-AML. All this explains why research on t-MDS and t-AML is a rather slowly progressing area in the field of medical oncology and why it is important, in addition to the single institution studies, as demonstrated in the following articles also to survey the overall experience.

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