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EDITORIAL

Therapy-related acute myeloid leukaemia with mutated *NPM1*: treatment induced or *de novo* in origin?

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Acute myeloid leukaemia (AML) carrying *NPM1* mutations that cause aberrant cytoplasmic expression of nucleophosmin,[1,2] accounts for about one-third of *de novo* adult AML (50–60% of AML with normal karyotype), and shows distinctive biological and clinical features.[3] Until now, little information was available on the incidence of *NPM1* mutations in therapy-related AML (t-AML) or on the molecular and clinical characteristics of t-AML with mutated *NPM1*.[1,4–6] Thus, the first comprehensive study of t-MDS (t-myelodysplasia)/t-AML with mutated *NPM1* reported by Andersen *et al*.[7] in this issue of the *Journal* is timely and remarkable.

Andersen *et al*.[7] observed that *NPM1* mutations occurred at lower frequency in t-AML than in *de novo* AML and were not related to any specific type of therapy. Notably, about 70% of the *NPM1*-positive t-MDS/t-AML had normal karyotype (an unusual finding in these cases, which generally show an abnormal karyotype) and none of them carried 7q−/−7, the most common abnormality in t-AML.[8] Finally, about half of t-MDS/t-AML with mutated *NPM1* expressed the *FLT3* internal tandem duplication.

These findings are of great relevance since they indicate that t-AML with mutated *NPM1* markedly differs cytogenetically and molecularly from other t-AML subtypes. Interestingly, normal karyotype and a high incidence of *FLT3* internal tandem duplication are both distinctive features of *NPM1*-mutated AML with *de novo* origin.[1] The finding by Andersen *et al*.[7] that two t-AML with mutated *NPM1* carried a ring chromosome 10 and a trisomy 8, respectively, is in keeping with the observation that about 14% of *de novo* AML with mutated *NPM1* harbour chromosomal aberrations, which are thought to be secondary.[1]

De novo AML with mutated *NPM1* shows a distinct immunophenotype[1] and gene expression profile,[9–11] which is characterized by CD34 downregulation (at RNA and protein levels) and upregulation of most *HOX* genes. Unfortunately, Andersen *et al*.[7] were not able to provide any information on the *HOX* gene signature and CD34 protein expression in their cases. However, the few *NPM1*-mutated t-AML with normal karyotype so far investigated were usually negative for the CD34 molecule,[4] suggesting they may have the same immunophenotype (and possibly the same molecular signature) as *NPM1*-mutated AML arising *de novo*.[1] Future efforts are warranted to clarify this issue.

Thus, although some information is still missing, the evidence strongly suggests that *de novo* and therapy-related *NPM1*-mutated AML share common biological features. This finding is hardly surprising since t-AML with other recurrent genetic abnormalities, such as t(15;17) inv(16) or t(8;21), usually show the same biological and clinical findings as *de novo* AML with the corresponding karyotypes.[12] Rather, it further supports the view that *NPM1* mutation is a founder genetic alteration, which defines a distinct leukaemia entity.[3]

The results from Andersen *et al*.[7] also raise the intriguing question of whether their t-AML cases with mutated *NPM1* are truly secondary leukaemias induced by previous treatment or whether they represent *de novo NPM1*-mutated AML arising in patients with a history of therapy. If *NPM1*-mutated t-AML is related to previous treatment, the close association with normal karyotype clearly indicates that the leukaemogenic mechanisms must differ from those that operate in t-AML carrying an abnormal karyotype. In t-AML with t(8;21) or t(15;17), DNA double breaks caused by drugs, especially topoisomerase II inhibitors, are thought to favour the development of balanced translocations.[13,14] However, the role of NPM1 mutants in the development of *de novo* AML still remains to be elucidated,[3] and, therefore, no causal relationship with previous treatment can be established at this time.

Conversely, like t-AML carrying internal-tandem duplication of the *MLL* gene,[15] it is conceivable that a significant fraction of the t-AML reported by Andersen *et al*.[7] are *de novo* leukaemias occurring incidentally in patients with a history of therapy. This is supported by the finding that these cases often received local radiotherapy or methotrexate plus prednisone, which are treatments whose leukaemogenic potential remains controversial. Moreover, two patients developed t-AML after unusually short or long latent periods. Another argument against these cases being secondary to therapy is that AML with mutated *NPM1* has been constantly associated with a *de novo* origin. Indeed, *NPM1* gene mutations are not usually observed in AML secondary to myelodysplasia or chronic myeloproliferative disorders,[1,3] and in-depth analysis of the only reported case of *NPM1*-mutated AML in this setting revealed a possible *de novo* origin.[16]

Therapy-related AML appears to be molecularly and clinically heterogeneous and its prognosis varies with the underlying genetic lesion. Cases harbouring 7q−/−7 genetic alterations are usually associated with poor prognosis, while t-AML carrying the t(15;17), t(8;21) or inv(16) translocations generally have a good outcome. Thus, whatever the nature of *NPM1*-mutated t-AML (therapy-related or arising *de novo*), future clinical studies should address the issue of whether t-AML with the *NPM1*-mutated/*FLT3* internal tandem duplication-negative genotype shows the same favourable prognosis as the corresponding *de novo* cases.

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B Falini
Section of Haematology and Immunology, Institute of Haematology, University of Perugia, Perugia, Italy
E-mail: faliniem @unipg.it

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