Acute leukemia arising after radioiodine treatment for thyroid cancer

In a recent paper, Schroeder and colleagues addressed the issue of secondary myeloid neoplasms after exposure to radioiodine (I-131) given for thyroid cancer and other indications.[1] This subject is of particular interest to us and we also analyzed the incidence and clinical characteristics of secondary leukemia arising after thyroid cancer treatment in our center (Institut Paoli Calmettes, Marseille, France). Between 1989 and 2010, 10 cases of secondary acute leukemia after radioiodine treatment were identified. This represents 2.5% of secondary acute leukemias (SAL) diagnosed in our center. We also identified 5 similar cases from a systematic review of the literature[2-5] and included their data in the present analysis (Table 1). Among the 15 patients, the majority were women (13 of 15) with a median age of 52 years (range 22-72 years) at the time of diagnosis of leukemia. All patients received I-131 after thyroidectomy (n=13) or for metastatic disease (n=2). None of them had been previously exposed to radiation or chemotherapy. The total dose of I-131 did not exceed 1000 mCi for any of the patients. The median time between I-131 and SAL diagnosis was 7.5 years (range 3 months-20 years). Pathological findings included 10 acute myeloid leukemias (AML), 2 promyelocytic leukemias (APL) and, interestingly, 3 acute lymphoblastic leukemias (ALL). Among the 10 other AMLs, 6 patients had unfavorable karyotype including 4 cases harboring del(5q) and one case harboring del(7q) and MLL rearrangement. Among the 3 patients with ALL, 2 presented a Philadelphia positive ALL with translocation t(9;22) and additional cytogenetic findings (including del 9q in one patient).

Interestingly, most of the data shown by Schroeder and colleagues were mostly consistent with our own findings. Nevertheless, due to the way in which patients were selected (use of the Dusseldorf MDS registry and queries sent to centers), a significant part of the clinical spectrum of secondary hematologic malignancies was not described. The existence of APL (20% of our cohort) has already been described in the literature, mostly with higher doses of radioiodine,[6] but is described here with lower doses of radiation. Furthermore, 3 cases of ALL are included in our study. The cytogenetic findings with 2 out of 3 cases with Philadelphia chromosome are consistent with secondary disease. Interestingly, the two Philadelphia positive ALL had very long latencies ranging from 10 to 20 years. The clinical presentation of this group of patients, which encompassed the whole spectrum of therapy-related leukemias, including a high proportion of APL and Ph positive ALL, is less common than that described for other malignancies.

As far as AL latency is concerned, our findings are in favor of a bimodal distribution with one peak at 1-3 years and a later peak at 8-10 years. Unfortunately, these data are not provided in the paper of Schroeder et al. but may be of some interest in terms of the cytological and cytogenetic profiles of these 2 sub-populations. The number of patients in our cohort did not allow us to clearly define these profiles ourselves. This is also an important point regarding the recommended follow up after radioiodine exposure because for at least 50% of the patients experiencing SAL as a late onset complication it may not have been reported that this was related to the thyroid cancer treatment. This means that clear information must be made available to patients exposed to this type of therapy and appropriate surveillance, including very long-term follow up, must be enforced over the years after treatment. Finally, we also noticed an increased female predominance for SAL (9 of 1) compared to that known for

Table 1. Patients' characteristics.

Patients	Age (years)	Sex	Time to SAL (years)	Thyroid surgery	Iodine therapy	WBC (G/l)	FAB classification	Karyotype	Treatment	Complete remission	Death
1	46	Female	8	Yes	Yes	22	M1	Normal	DNR + ARAC	Yes	Yes
2	70	Female	< 1	Yes	Yes	3	M2	Complex, Del 5q	Azacitidine	Yes	Yes
3	57	Female	13	Yes	Yes	1	M2	Del 7, t(11;14)	DNR + ARAC Lomustine	Yes	No
4*	34	Female	3	Yes	Yes	1	M2	Del 5q	DNR+ARAC	Yes	No
5*	48	Female	1	Yes	Yes	56	M2	47XX + 8	Mitoxantrone + ARAC + etoposide	Yes	No
6	39	Female	2	Yes	Yes	1	M3	t(15;17)	IDA+ ARAC ATRA	Yes	No
7*	43	Female	5	Yes	Yes	5	M3	t(15;17)	DNR+ARAC + ATRA	Yes	No
8	66	Female	< 1	Yes	Yes	25	M4	47 XX, +8	DNR+ARAC	Yes	No
9	71	Female	7	No	Yes	2	M5	Complex, del5q	DNR+ARAC	No	Yes
10	45	Female	8	No	Yes	20	M6	Normal	No treatment	Yes	Yes
11	82	Male	13	Yes	Yes	4	M6	Normal	Azacitidine	No	No
12*	44	Male	8	Yes	Yes	2	M6	Complex, del5q	DNR+ARAC	Yes	No
13	22	Female	2	Yes	Yes	63	B ALL	Normal	HyperCVAD	Yes	No
14	52	Female	10	Yes	Yes	2	B ALL	t(9;22)	hyperCVAD+ IM	Yes	No
15*	45	Female	20	Yes	Yes	4	B ALL	t(9;22)	HyperCVAD	No	Yes

*DNR: daunorubicin; ARAC: cytarabine; IDA: idarubicin; ATRA: trans retinoic acid; HyperCVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone; IM: imatinib mesylate; *cases from the literature.*

thyroid cancer (3 of 1).[6,7] We can only speculate about the potential mechanisms underlying these differences which may include polymorphism in DNA repair pathways, detoxification pathway or, considering the striking female predominance, maybe even hormonal pathways.

Overall, this work stresses the need for specific research programs focusing on the risk factors that influence the occurrence of SAL in cancer survivors. However, the possibility that the emergence of SAL can be connected just as much to environmental factors as to thyroid cancer cannot be excluded and larger scale studies may help us identify them.

To conclude, our data confirm those of Schroeder and colleagues, and strengthen the case for a longer and more detailed follow up for all patients with prior thyroid malignancy.

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Key words: acute leukemia, secondary neoplasms, radioiodine, thyroid cancer.

Citation: Gilabert M and Prebet T. Acute leukemia arising after radioiodine treatment for thyroid cancer. Haematologica 2012;97(8):e28-e29. doi:10.3324/haematol.2012.067454

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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