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Hodgkin's disease and the risk of acute leukemia in successfully treated patients

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Today, for a patient diagnosed with Hodgkin's disease the chances of receiving a successful treatment have greatly improved to the point that cure can be achieved in a large fraction of patients. This goal has been reached through continuous clinical trials conducted over the last three decades. Paradoxically, this effort has also been of paramount importance in clearly demonstrating that some treatments used to control cancer have the potential to induce new primary malignancies.

The occurrence of a second primary malignancy may have several causes. In one and the same individual it may represent a chance occurrence, it may result from host susceptibility factors, it may be linked to common carcinogenic influences or a clustering of different risk factors, or it may represent an association with the treatment for the first tumor.[1] Of all the late complications of treatment, second malignancies are generally considered to be the most serious since they can threaten the life of patients potentially cured of their first cancer. Hodgkin's disease is probably the most extensively studied malignancy as far as therapy-related complications are concerned, and the risk of second cancers, especially acute non-lymphocytic leukemia (ANLL), has been actively studied since the early '70s.[2] ANLL was the first second cancer that was systematically reported, probably because of its relatively short latency period. Virtually every research group has reported their experience with second leukemias: overall, compared to the general population, the risk of ANLL has been reported to be 10- to 80-fold increased. Nevertheless, because of the rarity of this malignancy in the general population, this highly increased relative risk translates into a relatively low cumulative risk that ranges between 1.4% to 4.1% at 15 years from starting treatment for Hodgkin's disease.[3] In the various case series, the absolute excess risk has been estimated to vary between 9 and 30 excess cases per 10,000 patients per year.

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Although the relative risks of leukemia are quite high, leukemia is a rare outcome and individual case series from clinical trial databases have limited ability to examine all of the suspected cofactors in the development of this event. By contrast, population-based cancer registries, that have large number of patients available, have the disadvantage of limited data regarding detailed types of treatment delivered to each individual patient during the entire course of the disease.

The paper by Brusamolino *et al*.[4] published in this issue of the journal, represents an important source of information. Detailed data from patients with Hodgkin's disease diagnosed, treated and followed-up at the Institutes of Hematology of the Universities of Pavia and Rome were pooled together to constitute a fairly large database that allowed answers to specific questions on the risk of ANLL. Besides confirming that the risk of leukemia is very low (0.3%) after radiotherapy alone, Brusamolino *et al.* attempted to disentangle the leukemogenic effects of different drugs given in combination to treat their patients. They found that a lomustine-based regimen given as salvage therapy after MOPP (mechloretamine, vincristine, procarbazine and prednisone) and ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) increased the risk of ANLL compared to MOPP alone, whether (15.6% vs 10.2%) or not (4.4% vs 2.2%) radiation therapy was also delivered. Despite the limited number of patients available, there is evidence that omitting mechloretamine or substituting this drug with cyclophosphamide decreases the risk of ANLL from 10.2% to 0.4-0.6%. Of importance, the authors confirm that with ABVD, or MOPP/ABVD, the risk of leukemia is almost non-existent (1 of 153 and 1 of 423, respectively), despite the fact that, very recently, evidence has accumulated that adriamycin and epirubicin, which are intercalating topoisomesare II inhibitors, may induce a type of ANLL similar to the one related to epipodophyllotoxin treatment.[5,6]

This study also confirms that duration of drug treatment and extent of radiation therapy can influence the risk of ANLL, despite the fact that most

probably the subgroup with prolonged drug therapy actually includes patients who received the lomustine-based chemotherapy for salvage treatment[4] and it is difficult to disentangle the contribution of each factor. The role of splenectomy in the etiology of treatment-related leukemia remains somewhat controversial. Since the initial report of the association published in 1987,[7] most large groups have evaluated their data, but results are contradictory. In the paper by Brusamolino *et al.*,[4] splenectomy appears to be influential only in patients treated with MOPP chemotherapy. This observation is in line with a recent report from the Dutch group that revealed a persistent 3-fold risk associated with splenectomy, but also reported preliminary evidence that the chemotherapy regimens currently in use appear to be associated with a lower risk of leukemia.[8]

The occurrence of treatment-related cancer is a major problem in patients who have probably been cured of their Hodgkin's disease. Increased knowledge of factors responsible for the occurrence of second cancers is of crucial importance for the development of new treatment strategies. Despite the greatly increased risk observed for several cancer sites, the issue of treatment-induced second cancers must always be viewed in relation to the dramatic increase of survival rates of patients with Hodgkin's disease. The short- and long-term risks of second malignancy, and of other complications, which are associated with a given treatment regimen should be weighed carefully against the consequences of not using such an approach, especially when this treatment is the only, or the best way to cure the patients. The arbitrary alteration of a successful therapy in order to reduce the risk of second cancers is unwarranted and it is of utmost importance that changes in therapy to reduce the risk of late complications be made only in the context of carefully designed clinical trials which can evaluate whether the overall treatment efficacy has not been compromised. In 1973 our group designed a regimen known as ABVD[9] which, in successive randomized studies, was found to have a similar, if not superior, efficacy than the time-honored MOPP chemotherapy.[10,11] The study reported by Brusamolino *et al*.[4] confirms preliminary data[2] that ABVD-based regimens are far less leukemogenic than MOPP and that it is indeed possible to reduce the risk of ANLL while maintaining equal levels of therapeutic effectiveness. It is hoped that the reduction of dose and fields of irradiation, as applied in several recent trials, will results in a lower risk of solid tumors which, in long-term follow-up (i.e. >10 years), represent most of the excess risk of second malignancies and an additional complication of modern treatment modalities.[12]

References

1. Boice JD Jr, Storm HH, Curtis RE, et al. Introduction to the study of multiple primary cancers. Natl Cancer Inst Monogr 1985; 68:3-9.
2. Valagussa P, Bonadonna G. Carcinogenic effects of cancer treatment. In: Peckam N, Pinedo H, Veronesi U, eds. Oxford Textbook of Oncology. Oxford: Oxford University Press; 1995. p. 2348-58.
3. Valagussa P. Second neoplasms following treatment of Hodgkin's disease. Curr Opin Oncol 1993; 5:805-11.
4. Brusamolino E, Anselmo AP, Klersy C, et al. The risk of acute leukemia in patients treated for Hodgkin's disease is significantly higher after combined modality programs compared to chemotherapy alone and correlates with extension of radiotherapy and type and duration of chemotherapy: a case control study. Haematologica 1998; 83:812-23.
5. Pedersen-Bjergaard J, Sigsgaard TC, Nielsen D, et al. Acute monocytic or myelomonocytic leukemia with balanced chromosome translocation to band 11q23 after therapy with 4-epi-doxorubicin and cisplatin or cyclophosphamide for breast cancer. J Clin Oncol 1992; 10:1444-51.
6. Sandoval C, Pui CH, Bowman LC, et al. Secondary acute myeloid leukemia in children previously treated with alkylating agents, intercalating topoisomerase II inhibitors, and irradiation. J Clin Oncol 1993; 11: 1039-45.
7. van Leeuwen FE, Somers R, Hart AA. Splenectomy in Hodgkin's disease and second leukaemias [letter]. Lancet 1987; 2:210-211.
8. van Leeuwen FE, Chorus AMJ, van den Belt-Dusebout AW, et al. Leukemia risk following Hodgkin's disease: relation to cumulative dose of alkylating agents, treatment with teniposide combinations, number of episodes of chemotherapy, and bone marrow damage. J Clin Oncol 1994; 12:1063-73.
9. Bonadonna G, Zucali R, Monfardini S, et al. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine and imidazol carboxamide versus MOPP. Cancer 1975; 36:252-9.
10. Bonadonna G. Modern treatment of malignant lymphomas: a multidisciplinary approach? The Kaplan Memorial Lecture. Ann Oncol 1994; 5 (Suppl 2): S5-S16.
11. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 1992; 327:1478-84.
12. Maurizi Enrici R, Anselmo AP, Osti MF, et al. Analysis of the risk of solid tumor following Hodgkin's disease. Haematologica 1997; 82:57-63.