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Do children have increased susceptibility for developing secondary acute myelogenous leukemia?

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Abstract

This study was undertaken to evaluate the effects of age on a child's susceptibility to developing leukemia following exposure to known leukemogenic agents. The clinical literature describing the risk of developing acute myelogenous leukemia (AML) following treatment with alkylating agents or topoisomerase reactive drugs (known leukemogens) was used as a basis for this investigation. Based on this preliminary assessment, the age of the child does not appear to be an independent variable for risk following treatment with either class of drug. Although the number of studies and cases was very small, the available scientific and medical literature does not support the hypothesis that children will necessarily have an altered susceptibility or increased risk of developing chemotherapy-induced AML.

Keywords: Secondary acute myelogenous leukemia; Benzene; Children

1. Introduction

Increasing attention is being placed on children's health issues and potential adverse effects following children's exposure to toxic chemicals. This heightened scrutiny has come from regulators, drug companies, researchers and clinicians alike. Secondary acute myelogenous leukemia (s-AML) is a well-recognized clinical entity, often the unfortunate consequence of treatment with certain classes of cytotoxic chemotherapy (in this context, it is often referred to as therapy related AML or t-AML). Drugs known to cause AML following therapy for a primary malignancy are generally alkylating agents and/or topoisomerase II inhibitors. While t-AML occurs following treatment with high dose radiation or chemotherapy, there has been concern that it might also occur in children following exposure to certain environmental toxicants such as benzene.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukaemia; HD, Hodgkin disease; MOPP, nitrogen mustard, vincristine, procarbazine, prednisolone

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While benzene is a known occupational leukemogen, there are very few data on the adverse health effects of environmental levels of benzene, which are typically orders of magnitude lower than what is found in the workplace. Nonetheless, speculation exists that children may have altered susceptibility to low levels of benzene and consequently be at potentially greater risk than adults of developing leukemia from environmental exposures.

The primary purpose of this analysis was to provide information that may be useful in understanding benzene-induced leukemogenic risk in children. However, there have been no documented cases of benzene-induced leukemia in children. Therefore, in the absence of benzene specific data, another known etiological agent for AML in children was used as a surrogate. Data which allowed for an evaluation of the effect of age on a child's risk of developing secondary leukemia were found in the cytotoxic chemotherapy literature. Several studies were located that reported treatment of different-aged children with the same disease with potentially leukemogenic drugs.

The literature on the treatment of Hodgkin lymphoma (Hodgkin disease (HD)) was used to evaluate age specific risk of developing t-AML following treatment with alkylating agents. The disease is known to occur in both adults and children and was treated similarly in all age groups (chemotherapy doses are normalized to surface area and occur with or without radiation). The most commonly reported treatment protocol reported in these studies was nitrogen mustard, vincristine, procarbazine, prednisolone (MOPP). The clinical literature on the therapeutic management of acute lymphoblastic leukemia (ALL) was used to evaluate the effects of age on risk of developing t-AML following treatment with topoisomerase reactive drugs. These two classes of leukemogenic drugs are known to act via different mechanisms and whether or not they represent an appropriate surrogate for benzene-induced AML is subject to debate. Nonetheless, this literature represents a source of published data regarding the risk of children developing chemically-induced leukemia.

Treatment protocols varied considerably across studies, making some comparisons difficult (or impossible). Therefore, only studies with well-defined treatment protocols and age related data were used. Chemotherapy doses were normalized according to patient body mass (or surface area) and descriptions of the treatment protocols at each institution were carefully analyzed. A key assumption inherent to this analysis is that chemotherapy-induced AML can provide relevant information regarding benzene-induced AML. With cautious interpretation, we believe this approach provides a reasonable foundation upon which to understand the effect of age on chemotherapy-induced leukemogenic risk and potentially provide insight regarding benzene specific risks.

2. Pathological characteristics of two common forms of t-AML

2.1. Alkylating agents

It is generally recognized within the hematology and medical communities that treatment of primary malignancies with drugs that act as alkylating agents are capable of leading to myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia [1]. This list includes, but is not limited to, melphalan, chlorambucil, busulfan, cyclophosphomide and nitrosourea compounds. Since most modern therapeutic regimens utilize a combination of drugs, it is often difficult to discern the precise offending agent. Nonetheless, as a class, there can be little doubt that treatment with these drugs alone or in various chemical 'cocktails' increases the risk of developing t-AML. The exact risk is not known but has been reported to be as high as 15–20% in some series, with the relative risk approaching 100 in many studies.

It is also clear that AML arising secondary to treatment with alkylating chemotherapeutic agents is a clinical entity that is distinct from AML arising de novo, or primary, which has no readily identifiable cause [2,3]. One hallmark of t-AML is the involvement of recognizable cytogenetic lesions, specifically the loss of part or all of chromosomes 7 and/or 5 [4]. It has been estimated that cytogenetic lesions involving chromosomes 7 and/or 5 occur 85–95% of the time in AML arising secondary to alkylating agents [5]. In contrast, deletions of chromosome 5 and/or 7 occur much less frequently in primary AML [6,7]. Another distinguishing characteristic of t-AML is that it is often, perhaps invariably, preceded by MDS [8–10].

2.2. Topoisomerase inhibitors

Clinical studies have also revealed that a different form of AML can arise secondary to treatment with drugs that primarily target topoisomerase II, an enzyme required for DNA replication [11–15]. Etoposide, teniposide and other epipodophyllotoxins as well as anthracycline-based antibiotics such as doxorubicin have been implicated in the etiology of this form of secondary leukemia [11]. The most common cytogenetic abnormality in AML secondary to agents that target topoisomerase II is 11q23 (30–60%) [14,15]. Occasionally, balanced translocations are reported in these patients similar to those seen in de novo leukemia [14]. AML secondary to treatment to topoisomerase inhibitors present with a distinct clinical picture compared to t-AML associated with high dose alkylating therapy. Leukemia secondary to topoisomerase II inhibition or radiation has a shorter latency (6–36 months) and the absence of a preceding myelodysplasia [11,16]. The cytogenetic lesions are often the same as in de novo leukemia and the disease is equally responsive to treatment (t-AML following alkylating therapy is highly refractory to treatment) [14]. These characteristics are briefly summarized in Table 1.

AML cases in workers occupationally exposed to benzene, where appropriate analysis has been conducted, appear to possess a constellation of cytogenetic and morphological characteristics reminiscent of AML arising following treatment with alkylating agents and typically lack features associated with t-AML associated with topoisomerase II inhibition [3,17–23].

Table 1
Pathological characteristics of t-AML

Alkylating agents	Topoisomerase inhibitors
Preceding myelodysplasia	No myelodysplasia
Cytogenetic aberrations involving chromosomes 5 and/or 7	Frequent involvement of chromosome 11 (11q23) and MLL gene
Refractory to treatment	As treatable as de novo AML
Long latency (2–10 years or more)	Short(er) latency (6 months–2 years)

3. Results

Pui et al. evaluated the risk of t-AML in children and young adults treated for HD with MOPP therapy [24]. The patients in this study were classified into two age 'bins', 0–12 and 12–20 years of age. As can be seen in Fig. 1, there were no reported cases of t-AML following treatment in children aged 0–12 years ($N = 153$). In contrast, 2% of older patients ($N = 294$) developed t-AML following MOPP treatment [24]. Long-term survival was similar between the two groups. Similar results were reported by Tucker et al., where the absolute excess risk of t-AML following MOPP treatment rose progressively with the age of the patient (Fig. 2) [25]. These two studies suggest that younger children might actually have decreased risks compared to older children and young adults [25]. Fig. 3 demonstrates the risk of t-AML in adults with HD treated with MOPP therapy. While the actual percentage varies considerably between individual studies, the range of adults treated for HD that develops

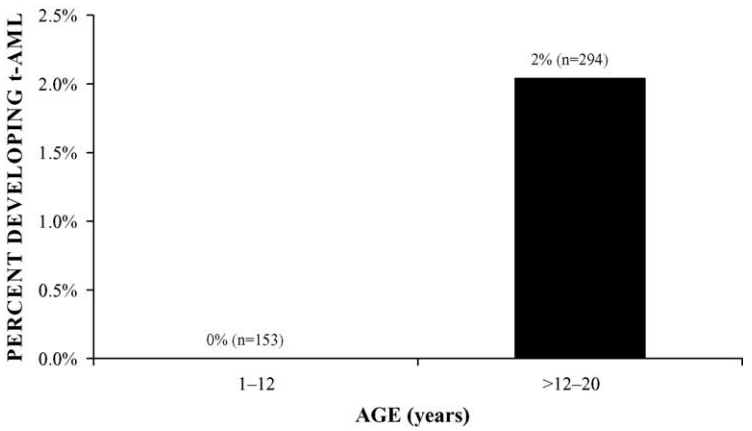

Fig. 1. Percentage of children and young adults that developed t-AML following treatment for HD (Pui et al. [24]).

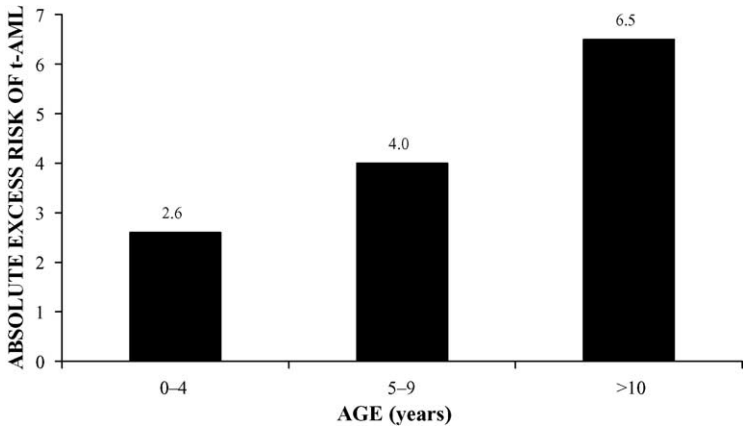

Fig. 2. Absolute excess risk of developing t-AML in children of various ages following treatment for HD (Tucker et al. [25]).

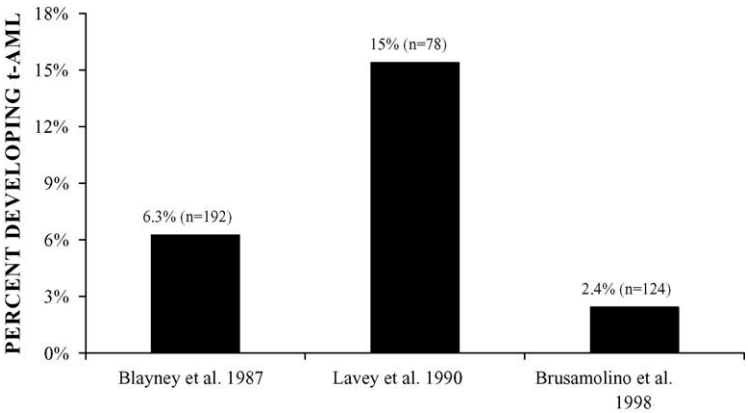

Fig. 3. Percentage of adults that developed t-AML following treatment for HD. Data from representative studies demonstrating reported ranges [7].

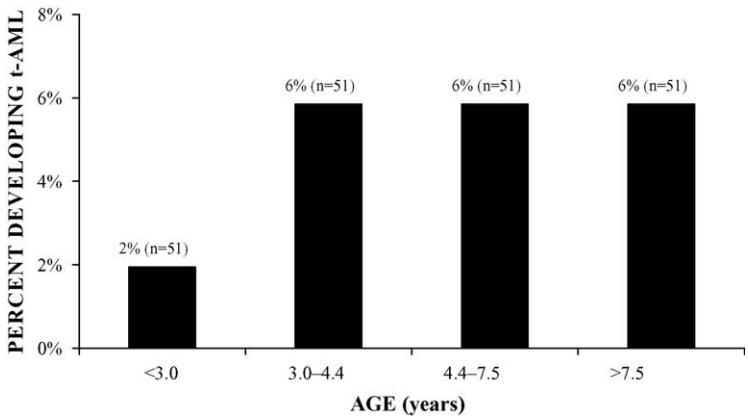

Fig. 4. Percentage of children of various ages that developed t-AML following treatment for ALL (Winick et al.[26]).

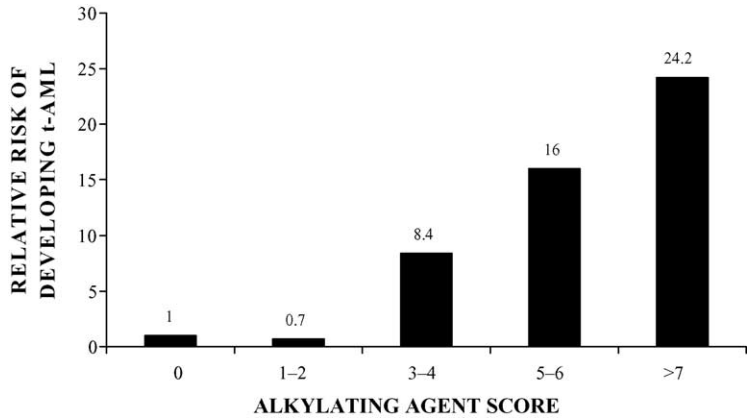

Fig. 5. Dose response for risk of t-AML in children following treatment with increasing doses of alkylating (Tucker et al. [25]).

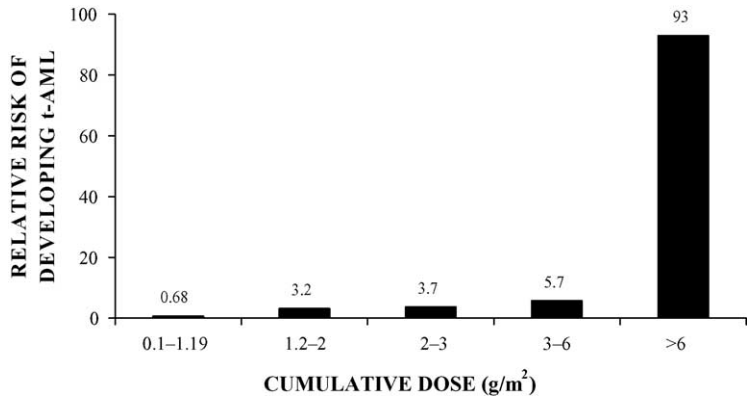

Fig. 6. Dose response for risk of t-AML in children following treatment with increasing doses of topoisomers inhibitors (Winick et al. [26]).

t-AML was comparable to that reported for children [7].

Winick et al. reported the absolute risks of developing t-AML in children treated with etoposide (and other drugs) for ALL. As can be seen in Fig. 4, there was no age related effect evident, with the exception that very young children (<3 years) had a slightly lower incidence rate of t-AML [26]. This was consistent with results reported for alkylating agents. Figs. 5 and 6 indicate that chemotherapy-induced leukemia (from both classes of leukemogenic therapy) in children follows a predictable dose–response, with increasing risk associated with increasing cumulative doses. This supports the hypothesis that the observed AML was secondary to treatment of the primary malignacies [25,27]. Since the studies used in this analysis normalized the dose as a function of surface area (and thus body weight), differences in dose are not likely to be a factor in this analysis. Fig. 5 was taken from Tucker et al., who calculated an 'alkylator score' based on the dose and potency of the drugs used [25].

4. Conclusions

This preliminary study was undertaken to evaluate the effects of age on a child's susceptibility to developing leukemia following exposure to known leukemogenic agents. As previously discussed, the primary intent of this analysis was to provide qualitative information potentially useful in understanding

benzene-induced leukemogenic risk in children. However, a direct comparison between children and adults with regard to leukemogenic risk from benzene exposure is not possible. Therefore, acute myelogenous leukemia arising secondary to chemotherapy was used as a surrogate to evaluate the effects of age on leukemogenic risk.

Based on Hodgkin disease studies, there is no evidence that younger children have an increased susceptibility to developing t-AML following alkylating therapy (MOPP). This was also true for children with ALL treated with topoisomerase II-reactive drugs. Additionally, these and other studies clearly indicate that the induction of iatrogenic leukemias exhibit a dose–response, with risks increasing with increasing dose. These studies also indicate that there is a dose of these known leukemogenic drugs whose risk of inducing t-AML cannot be distinguished from background risks. There is no reason to believe a priori that benzene would behave differently.

Only a small number of published studies and cases could be identified to support this comparison. Nonetheless, it was based on actual data (not hypothetical risk calculations) regarding childhood risks of developing leukemia. This analysis could be expanded to include non-published data from various cancer centers to increase the sample size, facilitating a more rigorous statistical comparison. An expanded study could have important implications, from both a regulatory as well as a pediatric oncology point of view. However, even in the absence of an expanded study, the existing data obtained from the published literature forms a reasonable foundation for a qualitative comparison. From the preliminary investigation presented herein, it does not appear that children are at increased risk of developing t-AML following treatment with leukemogenic drugs. If one accepts the premise that chemotherapy-induced AML is a reasonable model for benzene-induced AML, then this data also suggests that children would not have an increased risk of developing AML following benzene exposure.

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References

[1] J.H. Jandl, Blood, Textbook of Hematology, Little, Brown & Company, Boston, 1997.
[2] C.A. Coltman, S. Dahlberg, Treatment-related leukemia, N. Engl. J. Med. 322 (1990) 52–53.
[3] D.J. Park, H.P. Koeffler, Therapy-related myelodysplastic syndromes, Semin. Hematol. 33 (1996) 256–273.
[4] J.D. Rowley, M.M. Le Beau, Cytogenetic and molecular analysis of therapy-related leukemia, Ann. N.Y. Acad. Sci. 567 (1989) 130–140.
[5] B. Johansson, F. Mertens, S. Heim, U. Kristoffersson, F. Mitelman, Cytogenetics of secondary myelodysplasia (sMDS) and acute nonlymphocytic leukemia (sANLL), Eur. J. Haematol. 47 (1991) 17–27.
[6] J.D. Rowley, H.M. Golomb, J.W. Vardiman, Non-random chromosome abnormalities in acute leukemia and dysmyelopoietic syndromes in patients with previously treated malignant disease, Blood 58 (1981) 759–767.
[7] G. Leone, L. Mele, A. Pulsoni, F. Equitani, L. Pagano, The incidence of secondary leukemias, Haematologica 84 (1999) 937–945.
[8] T.B. Mallory, E.A. Gall, W.J. Brickley, Chronic exposure to benzene (benzol). III. The pathologic results, J. Ind. Hyg. Toxicol. 21 (1939) 355–377.
[9] M.S. Linet, S.N. Yin, L.B. Travis, C.Y. Li, Z.N. Zhang, D.G. Li, N. Rothman, G.L. Li, W.H. Chow, J. Donaldson, M. Dosemeci, S. Wacholder, W.J. Blot, R.B. Hayes, Y.Z. Wang, T.R. Dai, X.J. Chao, C. Qing, Z.L. Jiang, W.U. Zhang, P.Z. Ye, Q.R. Kou, Y.H. Fan, X.C. Zhang, Clinical features of hematopoietic malignancies and related disorders among benzene-exposed workers in China, Environ. Health Perspect. 104 (Suppl. 6) (1996) 1353–1364.
[10] R. Snyder, G.F. Kalf, A perspective on benzene leukemogenesis, Crit. Rev. Toxicol. 24 (1994) 177–209.
[11] M. Beaumont, M. Sanz, P.M. Carli, X. Maloisel, L. Thomas, P. Fenaux, Therapy-related acute promyelocytic leukemia, J. Clin. Oncol. 21 (2003) 2123–2137.
[12] L. Hoffmann, P. Moller, J. Pedersen-Bjergaard, A. Wagge, M. Pedersen, F.R. Hirsch, Therapy-related acute promyelocytic leukemia with *t*(15;17)(q22;q12) following chemotherapy with drugs targeting DNA topoisomerase II. A report of two cases and a review of the literature, Ann. Oncol. 6 (1995) 781–788.
[13] M. Anderson, R. Larson, N. Mauritzson, S. Schnittger, S. Jhanwar, J. Pedersen-Bjergaard, Balanced chromosome abnormalities inv(16) and *t*(15;17) in therapy-related myelodysplastic syndromes and acute leukemia: report from an international workshop, Genes Chromosomes Cancer 33 (2002) 395–400.
[14] A. De Renzo, L.F.E. Santoro, R. Notaro, F. Pane, M.R. Buonaiuto, L. Luciano, B. Rotoli, Acute promyelocytic leukemia after treatment for non-Hodgkin's lymphoma with drugs targeting topoisomerase II, Am. J. Hematol. 60 (1999) 300–304.
[15] J. Pedersen-Bjergaard, M.K. Andersen, D.H. Christiansen, C. Nerlov, Genetic pathways in therapy-related myelodysplasia and acute myeloid leukemia, Blood 99 (2002) 1909–1912.
[16] D.T. Bowen, Oxidative stress and the myelodysplastic syndromes, Leuk. Res. 24 (2000) 139–140.

[17] D.J. Paustenbach, P.S. Price, W. Ollison, C. Blank, J.D. Jernigan, R.D. Bass, H.D. Peterson, Re-evaluation of benzene exposure for the pliofilm (rubberworker) cohort (1936–1976), J. Toxicol. Environ. Health 36 (1992) 177–231.

[18] L. Rushton, H. Romaniuk, A case–control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom, Occup. Environ. Med. 54 (1997) 152–166.

[19] M.B. Paxton, V.M. Chinchilli, S.M. Brett, J.V. Rodricks, Leukemia risk associated with benzene exposure in the Pliofilm cohort: I. Mortality update and exposure distribution, Risk Anal. 14 (1994) 147–154.

[20] O. Wong, Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene, Occup. Environ. Med. 52 (1995) 380–384.

[21] L. Zhang, D. Eastmond, M. Smith, The nature of chromosomal aberrations detected in humans exposed to benzene, Crit. Rev. Toxicol. 32 (2002) 1–42.

[22] M.T. Smith, L.P. Zhang, Y.X. Wang, R.B. Hayes, G.L. Li, J. Wiemels, M. Dosemeci, N. Titenko-Holland, L.Q. Xi, P. Kolachana, S.N. Yin, N. Rothman, Increased translocations and aneusomy in chromosomes 8 and 21 among workers exposed to benzene, Cancer Res. 58 (1998) 2176–2181.

[23] L.P. Zhang, N. Rothman, Y.X. Wang, R.B. Hayes, W. Bechtold, P. Venkatesh, S.N. Yin, Y.Z. Wang, M. Dosemeci, G.L. Li, W. Lu, M.T. Smith, Interphase cytogenetics of workers exposed to benzene, Environ. Health Perspect. 104 (Suppl. 6) (1996) 1325–1329.

[24] C. Pui, M. Hancock, S. Raimondi, D. Head, E. Thompson, J. Wilimas, L. Kun, L. Bowman, W. Christ, C. Pratt, Myeloid neoplasia in children treated for solid tumours, Lancet 336 (1990) 417–421.

[25] M. Tucker, A. Meadows, J. Boice, M. Stovall, O. Oberlin, B. Stone, J. Birch, P. Voute, R. Hoover, J. Fraumeni, Leukemia after therapy with alkylating agents for childhood cancer, J. Natl. Cancer Inst. 78 (1987) 459–464.

[26] N.J. Winick, R.W. McKenna, J.J. Shuster, N.R. Schneider, M.J. Borowitz, W.P. Bowman, D. Jacaruso, B.A. Kamen, G.R. Buchanan, Secondary acute myeloid leukemia in children with acute lymphoblastic leukemia treated with etoposide, J. Clin. Oncol. 11 (1993) 209–217.

[27] M. Deley, T. Leblanc, A. Shamsaldin, M. ARaguin, B. Lacour, D. Sommelet, A. Chompret, J. Cayuela, C. Bayle, A. Bernheim, F. Vathaire, G. Vassal, C. Hill, Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthrcyclines: a case–control study by the Societé Francaise d'Oncologie Pediatrique, J. Clin. Oncol. 21 (2003) 1074–1081.