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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].