Benzene-induced acute myeloid leukemia: A clinician's perspective

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Benzene-induced acute myeloid leukemia (AML) is considered a secondary form of AML, based both in theory and on limited cohort observations. Its latency, cytogenetic aberrations, and clinical features are thought similar to, or identical with, AML resulting from the use of modern day cytotoxic agents for chemotherapy and immunotherapy. Although distinction between secondary AML and the far more common de novo AML is difficult to establish with certainty in any given case, latency from toxic therapeutic and environmental exposure and certain clinical and pathological features generally separate these two entities. AML is the only human neoplasm proven to be potentially caused by benzene, which actually is an obsolete form of chemotherapy. Despite many years of environmental regulation, alleged toxic exposure to this ubiquitous chemical has become an expanding area of litigation. A review of benzene-induced AML suggests that, in developed countries, this entity should no longer merit serious consideration among workers in the modern petrochemical industry and related fields. Am. J. Hematol. 82:826–830, 2007. © 2007 Wiley-Liss, Inc.

Introduction

Toxic tort claims, particularly involving malignancies alleged to be caused by workplace exposure to benzene, is a growing area of litigation in which physicians are becoming more and more involved. Benzene has been a particular favorite for plaintiff's attorneys to implicate because it is ubiquitous in nature, often present in measurable amounts in various petrochemical products and in the environment, and is known to have the potential to cause human cancer. Current allegations of causation have expanded to include a variety of hematologic malignancies and other cancers. Nevertheless, only acute myeloid leukemia (AML) and certain forms of myelodysplasia (MDS) are proven to be potentially benzene-related [1,2]. Primary care physicians and hematologists/oncologists are often the sounding-board for their patients, and, on occasion, for attorneys, who seek specific information about disease causation. Those physicians should be conversant with the scientific literature surrounding benzene-induced AML, and the general distinction between secondary and de novo forms of AML and MDS, which are the subjects of this review.

Discussion

The term secondary leukemia is often employed to indicate forms of AML evolving either from pre-existing MDS, or developing as a consequence of exposure to environmental or therapeutic toxins or to radiation [3]. It is distinguished, by certain clinical and laboratory features, from the more common de novo AML, which may develop abruptly in members of the general population, and without known cause. MDS is a classification of heterogenous hematological disorders, of which some, but not all, may also be induced by environmental toxic exposures. Other conditions known to be associated with an increased incidence of AML are listed in the Table I.

Dose and latency

Two features of primary importance in assessing the relationship between an exposure to an environmental or therapeutic toxin and the consequent development of a secondary form of AML are the dose received and the latency, or elapsed interval between accumulation of a dose with sufficient potential to cause AML, and the actual appearance of the disorder. Among examples of chemotherapy-induced, secondary AML, the cumulative dose, given either orally or intravenously (rather than peak levels achieved after a single pulse administration), determines the incidence of secondary AML [3–6]. Information on latency is also best known through study of literally thousands of cases of secondary AML after administration of various types of chemotherapeutic agents with the ability to damage DNA. This chemotherapy model for latency is especially accurate and reproducible, not only because of the large number of cases studied, but also because the initial dose and final administration of chemicals are typically spaced only several months apart. Therefore, whether one chooses to define latency from the date of administration of either the first, or of the last dose of the chemical (s), to the onset of secondary AML, the calculated latency period will vary by only a few months.

The latency period between benzene exposure and secondary AML is not as accurately defined as it is with the use of modern chemotherapeutic agents, because most benzene-exposed cohorts identify only a very few suspected examples of secondary AML. Moreover, many of these cases were diagnosed years ago, before industrial chemical safety controls were improved, and the specifics of their leukemia classification were imprecise and with the absence of modern chromosomal analytic techniques. This lack of specific information has also contributed to the uncertainty and speculation about the specific mechanisms of human leukemogenesis by benzene. Nevertheless, examination of the available data suggests that the latency periods and the other clinical features of benzene-induced secondary AML and modern day chemotherapy-induced secondary AML can be considered analogous or identical [7–18].

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TABLE I. AML—Known Predisposing Associations

Chromosomal instability or aberration (i.e., Downs syndrome, familial acute myeloid leukemia)
Radiation exposure
Cytotoxic chemotherapy
Environmental toxins (i.e., benzene, arsenic, cigarette smoke)
Myelodysplastic syndromes
Myeloproliferative disorders
Pernicious anemia
Recovery from aplastic anemia
Paroxysmal nocturnal hemoglobinuria

There is a characteristic window of opportunity to develop secondary AML following a toxic exposure that is generally described as around 2–10 years [3,7,9,18–22]. For postchemotherapy AML (t-AML) the latency period from final dose is, in part, dependant upon the time interval during which the necessary cumulative dose is administered, and may be shorter than 2 years after intense, brief chemotherapeutic regimens [6]. Additionally, depending upon the mechanism of action of the specific chemical administered (for example, topoisomerase II inhibitor vs. alkylating agent), this latency interval may be closer to the shorter or to the longer end of the 2–10 year span [3–8,18–21].

Mechanism of leukemogenesis

Many authors have considered secondary AML developing as a consequence of either chemotherapy exposure or benzene toxicity to be quite similar, or even identical. This is not surprising since, in reality, benzene was employed as an early chemotherapeutic agent, administered orally in an olive oil base at doses of 2–5 g daily. It was particularly effective in the treatment of chronic forms of leukemia and polycythemia vera [23,24]. Its administration over several weeks could lower an elevated total leukocyte count from the 200,000 to 400,000/mm^3 level to the normal range, much like chronic oral therapy with the later-introduced alkylating agents. Persistent bone marrow damage, and even aplastic anemia, following its prolonged administration, was well-known. Arsenical and radioactive compounds were similarly used as early forms of chemotherapy [25]. Linking the potential hematologic consequences of chemotherapy, benzene, and other environmental toxins, Smith et al. comment, "The AML cases arising after DNA-damaging chemotherapeutic agents and the AML cases caused by diverse environmental factors (e.g., benzene, petroleum, organic solvents, and arsenical pesticides) are genotypically similar; the majority are characterized by deletions of all or part of chromosomes 5 and/or 7…" [10].

Benzene has long been considered a radiomimetic agent similar to alkylating agents and radiation exposure in its effect on the hematopoietic system. In recent years, some have postulated that it might also cause secondary AML through the action of its metabolites, which have some antitopoisomerase II activity [26]. Although it is clinically well-accepted that benzene-induced AML may be associated with loss of genetic material from chromosomes 5 and 7, similar to alkylating agent toxicity, the importance of its potential for antitopoisomerase II activity as a cause of secondary AML, with alternate chromosomal aberrations such as balanced translocations, remains entirely speculative [7,8,11]. Benzene metabolites may reduce topoisomerase II activity in cell culture, but there is no direct evidence either in the laboratory or from clinical observations that such inhibition may lead to specific patterns of chromosomal aberrations in human myeloid cells, simulating the damage induced by modern-day chemotherapeutic topoisomerase II inhibitors. Nevertheless, we may read, "…findings in the literature to date indicate that benzene may act like both alkylating agent causing alterations in chromosomes 5 and 7, and a topoisomerase II inhibitor…" [11]. And, "…the genotoxic effects produced by BZ (*benzene*) and its metabolites are most consistent with inhibition of topoisomerase II or ribonucleotide reductase inhibition. The chromosome abnormalities in human leukemia produced therapeutically by topoisomerase II inhibition also implicate this mechanism in BZ (*benzene*)-induced leukemia." [8].

Chromosome analysis

While chromosome analysis currently cannot accurately separate de novo forms of AML from examples of secondary AML, the presence of any abnormalities, and the particular pattern of such aberrations identified in an individual case, not only offers clues to this distinction, but provides important prognostic and therapeutic information. Thus, in de novo AML, the conventional chromosomal analysis may be normal nearly 50% of the time, while in secondary forms of AML, including benzene-induced AML, chromosomal abnormalities may be easily demonstrable in the vast majority of cases [27–30]. In examples of secondary AML, loss of chromosomal material from the 5 and 7 chromosomes are the most commonly encountered findings, with detection of certain other aberrations, much less frequent [18]. For example, among 518 total cases of AML exhibiting the 8;21 translocation, from two combined series, 97% were thought to represent de novo AML [29,30]. In another, single institutional study of more than 300 cases of secondary AML, none had the 8;21 translocation [31]. Thus, the presence of the 8;21 translocation, in an appropriate clinical setting, strongly favors a diagnosis of de novo AML. Similarly, in a group of 672 cases with the promyelocytic form of AML, and the associated 15;17 translocation, less than 5% were thought to have secondary AML [32]. The inversion 16 chromosome is another typical marker for de novo AML, and is rarely present in secondary AML, and not documented as occurring in benzene-induced AML [5,28,32–33].

Response to therapy

Treatment of secondary AML has generally been less effective than treatment of de novo AML in achieving remission and in prolonging disease-free survival [18,32]. Importantly, this difference in response has not been noted in forms of AML bearing certain chromosomal aberrations, such as the 15;17 translocation in promyelocytic leukemia, the 8;21 translocation, and with the inversion 16 chromosome. Here the response to antileukemic therapy is similar to treatment of de novo AML with comparable chromosomal aberrations [31–33]. Thus, depending upon the particular chromosomal abnormality identified, a poor response to therapy may also suggest a secondary AML.

Myelodysplasia

Still another feature that may be helpful in distinguishing between de novo and secondary AML is the presence or absence of a period of MDS preceding the diagnosis of frank AML. In secondary AML, about two thirds of patients exhibit a period of MDS prior to the appearance of AML, while this phenomenon is lacking in de novo forms of AML, which typically occur abruptly [3,18,28,32]. The term MDS refers to what has become a frequently modified group classification of hematopoietic disorders that have in

common persistent cytopenias, particularly progressive anemia, and usually characterized by ineffective or disorderly hematopoiesis, and a variable tendency to eventuate in AML. Seemingly misunderstood by most epidemiologists, toxicologists, and attorneys, the illnesses classified within this heading are heterogenous, and are not segregated in the category of MDS to suggest a common etiology, clinical course, or response to specific therapy [21,32,34–38]. In fact, two well-known and stand-alone illnesses initially added to the MDS category, chronic myelomonocytic leukemia (CMML) and acquired idiopathic sideroblastic anemia (AISA), also referred to as refractory anemia with ringed sideroblasts, do not appear linked, epidemiologically, with benzene exposure [39–44]. In particular, AISA may actually comprise several distinct disorders [45]. A newly described subset of AISA appears to manifest the JAK2 V617 F mutation common to most patients with myeloproliferative disorders such as polycythemia vera and essential thrombocytosis [46]. Similar to AML, clonal chromosome abnormalities are typically easily identified in secondary forms of MDS but the karyotype may remain normal, at least initially, in about 38% of de novo examples of MDS [34].

The bone marrow histology in benzene-induced MDS and following chronic, high-level benzene exposure is only occasionally described. However, consistent and well-documented features include bone marrow hypoplasia, dyserythropoiesis including multinuclearity, but without ringed sideroblasts, and eosinophilia with abnormal-appearing eosinophils [12,46–48]. Essentially, this histopathology represents a type of hypoplastic MDS [13]. It seems likely that some of the early reports of cases described as benzene-induced aplastic anemia actually represented this form of MDS, since bone marrow biopsies, often necessary to confirm aplastic anemia, were not routinely performed until the 1960s.

Heavily benzene-exposed cohorts

Among the three major cohorts of benzene-exposed individuals with an increased development of secondary AML, perhaps the closest relationship with modern day latency observations are those that Aksoy described in Turkish "shoe workers" [48–49]. Here, the time interval between the first observation of leukopenia or pancytopenia in the ~28,000 benzene-exposed workers and the development of secondary AML was emphasized. Such leukopenia was often transient, as is commonly the case following administration of chemotherapy. The blood counts in this cohort often fully recovered prior to the leukemic event. In effect, Aksoy was demonstrating that the subject had received a truly myelotoxic dose of benzene and, thus, might have the potential for later development of secondary AML. On this basis, he claimed a 6-month to 6-year latency interval in these individuals. This type of calculation may underestimate the point in time when the necessary cumulative dose of benzene was achieved, and perhaps a transient period of leukopenia missed. But certainly, his observations closely correlate with those in modern chemotherapy data.

The so-called Chinese benzene study of ~74,000 factory workers with considerable potential for benzene and solvent exposures examined the time to the appearance of presumed secondary AML among those who began employment at any point during a particular 15-year interval [12,17]. In this study, latency was arbitrarily defined as beginning after 6 months of employment. Obviously, this definition of latency would create an overestimate of the true interval, particularly in individuals working throughout the 15-year period, since it might take several years of employment in this environment to reach the necessary cumulative dose. Moreover, in a study of this large size and duration, some of the observed cases of AML would be coincidental examples of de novo AML, rather than representing secondary AML. Nevertheless, observations of Hayes et al. in this study also mirrored the modern day chemotherapy data, with the latency period for the appearance of secondary AML averaging about 10 years. He specifically drew attention to the similarity of this latency estimate with the more precise modern chemotherapy data [17].

The third, often-cited heavily benzene-exposed cohort study comprising the United States Pliofilm factory worker group of about 1,800 individuals, defines latency to secondary AML in a fashion such that accurate conclusions on this subject may not be drawn or offer a fair comparison with any of the studies described earlier. In this cohort there were only seven benzene-exposed subjects with the later development of AML. Based on standard mortality rates, at least two cases do not necessarily represent benzene-induced AML—but which ones? The latency calculation by Rinsky et al. began with the first date of employment and ended with the diagnosis of AML [50]. However, some of these individuals were employed as long as 27–37 years, and it would be impossible to know when during this long interval the cumulative dose of benzene necessary to potentially cause secondary AML was actually achieved, and the time clock for latency began. For example, if one calculated the mean latency to AML of these seven individuals from the date of last exposure, the latency period is 8 years. Thus, comparing latency from benzene exposure, as defined by Rinsky et al., in the Pliofilm cohort, to modern postchemotherapy latency data, and claiming a difference, is like attempting to compare apples with oranges, as the saying goes, and cannot be definitive, particularly with a cohort this small.

Dose response

The cumulative dose of benzene sufficient to potentially cause AML is also a contested data point because of the lack of precise exposure measurements and the small number of presumed benzene-induced cases of secondary AML available for study. Based on the Pliofilm cohort described earlier, and where toxic exposure was primarily from pure benzene, estimates of the necessary cumulative leukemogenic dose range from 40 to more than 200 part per million (ppm) years [50–53]. Whatever this dose actually is, it must be extremely high, and unlikely to be achieved by those employed in modern industry in the United States. Thus, numerous extended cohort studies comprising hundreds of thousands of petrochemical workers with potential for benzene exposure, and employed in developed countries, have shown no statistically significant increase in the incidence of AML among those hired for the past several decades [53–64]. In one such recent long-term study of 2,266 workers directly involved in chlorobenzol chemical processing, their mean cumulative benzene dose was about 40 ppm years, and there was no statistically significant increase in AML noted [64]. There is no evidence that the low-dose benzene exposure the petrochemical workers in the modern era may experience is sufficient to cause AML [22,63].

Cigarette smokers are exposed to benzene concentrations 10 times the concentrations nonsmokers are exposed to, and long-term heavy smokers may have a cumulative dose of benzene as much as 3–6 ppm years [65]. Nevertheless, this dose is far too low to account for the increased incidence of AML, and other, as yet unknown mechanisms are assumed [66–67]. The specific morphologic and chromosomal characteristics of smoking-induced AML are not

known with certainty, but complex karyotypic aberrations are thought to be more likely and the chromosomal aberrations identified appear distinct from those induced by benzene exposure and previously discussed [66–71].

Conclusion

The classical circumstances that might support benzene as a potential cause of AML are (1) occurrence in the setting of certain forms of MDS, (2) a 5 or 7 chromosome defect, (3) a substantial exposure history with a cumulative dose of at least 40 ppm years during the preceding 10-year interval, and (4) a poor response to antileukemic chemotherapy. Additional etiologic considerations, such as heavy cigarette smoking, previous exposure to chemotherapy or radiation, or certain underlying constitutional disorders such as Down's syndrome or pernicious anemia, should be absent [7,65–75]. Nevertheless, no constellation of findings can as yet allow a certain differential diagnosis, which becomes particularly difficult to assess in the very elderly person with AML. This is because the occurrence of AML (and MDS) in the general population increases dramatically with advancing age, with incidence rates per million population of only 12 at age 20–44, of 42 at age 45–64, and as much as 150 at ages greater than 65 years [34,76]. Additionally, examples of so-called de novo AML/MDS of the elderly may exhibit chromosomal changes similar to those found in secondary AML in younger individuals, even without any specific history of potentially adverse environmental exposures, further complicating risk analysis [32,71,77]. The reasons for this finding remain speculative.

Aside from cigarette smoke, which may be responsible for 9% or greater of all AML, other environmental toxins as a cause of leukemogenesis are thought to be uncommon [22,35,78–79]. Perhaps no more than 15–20% of all cases of AML, including those consequent to underlying MDS, and treatment of previous malignancies, represent a secondary form of the disease [36,80]. Thus, just as the use of benzene as a chemotherapeutic agent remains only a historical footnote, so should benzene exposure not be considered a significant cause of AML among workers in the modern petrochemical industry and related fields [63].

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