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Benzene as a cause of lymphoproliferative disorders

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ABSTRACT

There is a long standing issue concerning the strength of evidence relating benzene to lymphocytic neoplasms. Because benzene is a known cause of human acute myelogenous leukemia there has been little reason for organizations such as the International Agency for Research on Cancer (IARC) or the US National Toxicology Program (NTP) to perform standard hazard identification reviews of benzene as a possible cause of other cancers such as lymphomas. Increased understanding of underlying mechanisms of carcinogenesis, as is reflected in the greater scope given to mechanistic evidence in assigning overall sufficiency of evidence for carcinogenicity by both IARC and NTP, suggests that the evidence supporting benzene as a cause of lymphoma likely has passed the threshold required for being listed as a known causal relationship. A broad range of genotoxic effects in the lymphocytes of benzene-exposed workers has been well documented, as has the role of chromosomal effects in carcinogenesis. There is also increasing evidence of a close relationship between lymphoid tumors and the types of myeloid tumors known to be caused by benzene. This includes the not infrequent finding of biphenotypic lineage as well as the formation of lymphoid as well as myeloid leukemias following chemotherapy. Studies of the mechanism of benzene toxicity are consistent with a relatively non-specific mechanism capable of producing multiple chromosomal changes, and there is evidence that the early hematopoietic stem cell, which is believed to be targeted by benzene in causing myeloid cancers, is also the progenitor of lymphocytic cell types. Furthermore, the classification of lymphomas has evolved so that non-Hodgkin lymphoma now includes such formerly distinct disorders as chronic lymphocytic leukemia and multiple myeloma, and there is less of a distinction between leukemia and non-leukemia forms of lymphoma.

1. Introduction

Benzene is accepted as a known cause of human acute myelogenous leukemia (AML) and its variants [1,2]. However, there has been less clarity as to whether benzene is capable of causing lymphocytic hematological neoplasms, including non-Hodgkin lymphoma (NHL), acute and chronic lymphatic leukemia, multiple myeloma and Hodgkin disease. Epidemiological evaluation of lymphoma in benzene-exposed cohorts has been complicated in part because lymphoma is a grab bag of multiple diseases of seemingly diverse etiology ranging from the presumed viral cause of Burkitt's lymphoma to immunosuppression caused by drugs or microbial agents. The goal of this manuscript is to apply to the question of whether benzene is a cause of human lymphatic tumors recent advances in understanding of lymphomas that has led to the reclassification of these disorders. The role of mechanistic evidence in determination of human chemical carcinogenicity will be considered, and some of the key epidemiological findings and the current understanding of benzene toxicology will be briefly reviewed. The focus is on the hazard identification question of whether benzene exposure at any dose can cause a human lymphoma. The levels of benzene associated with lymphoma or the shape of the dose response curve will not be considered.

The increased reliance on mechanistic evidence for classification of a potential human carcinogen is particularly pertinent to the issue of whether benzene should be considered to be a known cause of human lymphoproliferative disorders. Both IARC and NTP have increased the weight given to mechanistic evidence in characterizing the overall strength of the total evidence used to classify the potential for a chemical or an exposure to be causal [3,4]. IARC now permits classification in Group 1, known human carcinogens, when there is less than sufficient evidence in humans but sufficient evidence in animals and "strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity" [3]. For many years there was substantial debate about whether benzene was a cause of human acute myelogenous leukemia (AML) and its variants. General acceptance of this causal relation occurred following a classic epidemiological study of a cohort of pliofilm workers in whom there was a 5-fold increase in risk of leukemia [5] In retrospect, the evidence for benzene as a myeloleukemogen from the earlier studies of Vigliani and Aksoy and others [6,7], as well as the mechanistic information of overt chromosomal damage pro-

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vided by Forni and co-worker [8], should have been viewed more seriously. These studies of heavily exposed shoe workers in Italy and in Turkey had an advantage, as compared to classic cohort epidemiological studies dependent upon death certificates, in that the clinical investigators observed the individual cases. Furthermore, had Aksoy or Vigliani used standard epidemiological approaches to age adjust their data, the evidence of benzene leukemogenesis would have been too overwhelming to reject; e.g., Aksoy's initial collection of AML cases in Turkey had a mean age of 32.4 years [7], while AML is usually a disease of individuals in their 60s or older. The unwillingness to accept the clinical studies and mechanistic findings delayed the protection of many workers from benzene toxicity [9].

2. Benzene as a cause of lymphoma in laboratory animals

A number of studies have shown benzene-induced lymphomas in laboratory animals. This includes classic long term exposure studies in which an increased incidence of lymphoma has been observed in various strains of mice, including a standard National Toxicology Program evaluation [10–13]. In a shorter exposure study, 125 CBA/Ca mice inhaling 300 ppm benzene for 6 h/day, 5 days/week for 16 weeks, and then held for 18 months, lymphomas were observed in 14 exposed mice and only 2 controls [14].

The NTP has recently reported on a study in which benzene was chosen to help evaluate new model systems for toxicology and carcinogenesis studies, in this case the haploinsufficient p16 Ink4a/p19 Arf mouse model [15]. Groups of 15 male and 15 female mice were treated with benzene by gavage at doses ranging from 0 to 200 mg/kg benzene for 27 weeks, far less than the usual long term study. As has been seen in other animal models, there was a marked decrease in the size of lymphatic tissues, including the thymus, spleen and lymph nodes, as well as a marked decrease in circulating lymphocytes. Bone marrow atrophy and anemia was noted, as was an increase in micronucleated red cells. An increase in malignant lymphomas was noted in male but not female mice receiving the highest benzene dose.

Recently, Kawasaki et al. [16] exposed Trp53-deficient C57BL/6 and C3H/He mice, as well as the wild type, to up to 300 ppm benzene 6 h/day, 5 days/week for 26 weeks. They found an increase in thymic lymphomas, NHL and AML [16]. It has been difficult to develop an animal model of benzene-induced AML, and it is pertinent that this now has been observed concomitantly with the presence of multiple types of lymphoma.

3. The changing classification of lymphomas

Changes in the WHO classification of lymphomas also greatly affect interpretation of the epidemiology of lymphatic tumors in relation to benzene causation. The new WHO classification, in which over 40 types of lymphoma are listed, clearly places such seemingly distinct disorders as multiple myeloma and chronic lymphocytic leukemia (CLL) within the family of NHL [17]. Many of these changes are based upon molecular biological findings allowing subclassification of the diseases. Others changes are based upon recognition of the similarity of the cell type and the natural progression of the disease. For example, most cases of CLL consists of small cell lymphocytes that are similar to those seen in a small B cell follicular lymphoma, and have the same relatively good prognosis – the only difference being whether the blood lymphocyte count is increased. The new WHO classification puts these two together as one disease. Similarly, it lists the classically aggressive B cell lymphocyte diseases as being in the unified disease category of "precursor B lymphoblastic leukemia/lymphoma", i.e., the same category whether these cells are present in the blood, where it has been known as acute lymphoblastic leukemia (ALL), or not present in the blood. T cell ALL is in a separate category, again combined with a pathologically similar non-leukemic T cell lymphoma. There is also a better understanding of the subtypes of Hodgkins lymphoma, including overlap with NHL [18]. This evolving understanding of lymphoma as a mixture of related diseases includes the recognition of the close relation between B cells and plasma cells, the latter being a specialized form of B cells. For example, the classic monoclonal protein spike observed in the serum of patients with multiple myeloma can also be seen in B cell lymphomas. The new classification, and the growing recognition of the biological basis for the overlap of the various lymphomas, complicates interpretation of epidemiological findings using previous classifications.

4. Genotoxicity of benzene

Benzene is the prototypic environmental chemical producing genotoxicity evident in circulating lymphocytes [19,20]. A variety of different effects have been identified; including micronuclei, abnormalities on the comet assay, and gross chromosomal abnormalities. Lymphocytes are known to be a target of benzene in laboratory animals and humans [21,22]. A decrease in circulating lymphocytes was found to be correlated with chromosomal hyperdiploidy of chromosome 9 ($p = 0.003$) in Chinese workers exposed to benzene [23].

Lymphocyte genotoxicity is now being used as a relatively common biomarker in studies of workers and the general population exposed to benzene [24–26]. Not all genotoxic endpoints are necessarily predictive of cancer. Further, cytogenetic findings in individual workers can be confounded by other causes [27]. However, genotoxicity in benzene-exposed workers extends to overt chromosomal abnormalities, such as hyperdiploidy, aneuploidy, translations and deletions that clearly are related to an increase in cancer risk [20,23]. The finding of genetic abnormalities in bone marrow precursor cells and in circulating lymphocytes is consistent with clastogenic events occurring in the myelolymphoid precursor cell. The toxicology of benzene is also consistent with multiple potential targets in the genome of bone marrow precursor cells. The evidence indicates that multiple metabolites of benzene act through one or more reasonably non-selective toxicity mechanisms that result in multiple chromosomal aberrations [20,28].

5. The relationship between myeloid and lymphoid hematopoietic neoplasms

The longstanding distinction between AML and ALL also has become somewhat blurred. First, the uncertainty as to whether there is a completely separate lineage for lymphocytic and myelocytic cells has been resolved in favor of recognition that the classic bone marrow pluripotential stem cell produces both lineages. Modern molecular tools developed to detect surface characteristics specific to the lymphoid or myeloid series have been very useful in distinguishing lymphoblasts from myeloblasts. But they have also shown that a few percent of leukemias are biphenotypic, containing surface markers of both lymphoblasts and myeloblasts [29]. In terms of pathogenesis, the distinction between AML and ALL also has been blurred by the recognition that either disease can occur in conditions that formerly seemed restricted to AML. These include ALL occurring in the acute leukemia seen in Down syndrome [30]; in secondary leukemias related to chemotherapy [31]; and the blast crisis of chronic myelogenous leukemia [32]. Similarly, the Philadelphia chromosome, long considered to be specific to chronic myelogenous leukemia, is also observed in a subset of ALL [10].

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6. Epidemiologic findings

The large epidemiological literature relating benzene to lymphomas has been inconsistent. Savitz and Andrews, in a 1997 review of the epidemiological evidence, found that most studies did not indicate a positive association between NHL and benzene, but pointed out many methodological limitations [33]. Similarly, Blair reviewing occupational exposures and NHL, stated that no occupational causes of NHL have been conclusively identified [34]. Chiu and Weisenburger and Alexander et al., in broad reviews of the epidemiology of NHL, noted the reported association of benzene with NHL but did not find the association conclusive [35,36]. Both called for future studies to incorporate the new WHO classification and molecular markers of disease.

In summary, one can cite studies that suggest a relationship between benzene exposure and NHL [37–40]; and studies which could be interpreted as not having shown an association [41–44]. As is true with any epidemiological study, each study is subject to interpretation based upon possible confounders, sufficiency of power, adequacy of exposure estimation, and all of the vagaries of chance associations. For example, Wong reported a relative risk for lymphopoietic cancer of 3.20 ($p < 0.05$) among male chemical workers exposed continuously to benzene as compared to an unexposed group, but pointed out the many problems which led the author to doubt the validity of the observed association [45]. Epidemiological studies of work forces are particularly problematic when the disease consists of multiple subtypes with presumably multiple etiologies and the classification of the disease is changing. As just one example of the issue posed by the WHO reclassification, previous studies that have shown an excess of chronic lymphocytic leukemia [46,47], should now be considered pertinent to the question of whether benzene is a cause of NHL – and note that CLL has not been shown to be increased in all cohorts [48,49]. Further, there is a special issue of a surveillance bias for CLL in benzene-exposed workers who routinely have blood counts [50].

Two sets of studies deserve particular attention in considering the epidemiological evidence associating benzene with NHL: those of Wong and Raabe [51] who evaluated a particularly large cohort of refinery workers specifically looking at the incidence of NHL; and that of the Berkeley group who recently have performed meta-analyses of studies relating benzene to NHL [52,53].

The study by Wong and Raabe of over 308,000 petroleum workers found a total of 506 deaths due to NHL with 561.68 expected, an SMR of 0.90 (95% CI 0.82–0.98) [51]. However, the study is not particularly pertinent to the hazard identification question of whether benzene can cause lymphoproliferative diseases. This is because the overall cohort was not reported to have an increase in AML, the hallmark cancer caused by benzene. This problem can be illustrated by considering the relevance to the potential question of whether cigarette smoking causes NHL of a study in which average smoking rates were so low that there was no increase in lung cancer. At most, as concluded by Wong and Raabe, petroleum workers were not at increased risk of NHL as a result of their exposure to benzene. But in the apparent absence of an increase in the risk of AML, it cannot be said that this study demonstrates that benzene exposure cannot cause lymphoma. In contrast, another issue presented by the Wong and Raabe study suggests that it actually supports the relationship between benzene and NHL. Their analysis of the different worker groups within this large study of petroleum workers reports what appears to be a statistically significant higher risk of NHL mortality among refinery workers than among distribution workers, who possibly have lower exposure to benzene than do those at the refinery (US refinery workers SMR 0.96; 95% CI 0.86–1.07; non-US refinery workers SMR 1.12; 95% CI 0.90–1.37; global distribution workers SMR 0.64; 95% CI 0.50–0.82 – note that there is no overlap in the confidence intervals between the upper end of the distribution workers and the lower ends of the two groups of refinery workers [51]). This significant difference could reflect the healthy worker effect for NHL. NHL is known to be caused by HIV and it is unlikely that those individuals with HIV or a high risk of HIV, e.g., intravenous drug users, are in the refinery workforce. NHL is also more common among those with inborn errors of their immune system and those receiving immunosuppressive therapy, again individuals who have a lesser likelihood of being employed.

In addition to the healthy worker effect there are a number of other potential impediments to the study of the relation between benzene exposure and lymphoproliferative disorders. These include the dilution of highly exposed individuals with those who are less exposed; latency period issues; and the outsourcing by the petrochemical industry of full time potentially high exposure jobs, such as millwrights who fix leaky valves or those who clean up after chemical spills, such that these individuals would not be part of a study of workers employed by the industry [54]. Recent work from a group at the University of California-Berkeley School of Public Health that supports an association between benzene and NHL has attempted to take a number of these issues into account. The authors reported that 40/43 case–control studies of NHL in those with probable benzene exposure show elevated risk; and that 23 of these 43 show statistical significance in this association [52]. A follow up by this same group reported that the relative risk increased when they excluded from their meta-analyses cohorts which likely included unexposed workers and when the healthy worker effect was taken into account. For all of their meta-analyses they reported a relative risk for NHL that was statistically significant before making these adjustments, and in all cases the adjustments led to higher levels of relative risk. In no case was the summary relative risk greater than 1.49 [53].

7. Conclusions

The biological plausibility of benzene as a cause of lymphoproliferative disorders has been strengthened in recent years by the further recognition that it is the same pluripotential stem cell at risk for benzene-induced AML that differentiates into both lymphocytic and myelocytic cell lines. Evidence continues to accumulate that the genotoxic action of benzene metabolites on these bone marrow precursor cells is reasonably non-specific, producing multiple genetic abnormalities. There are also additional studies demonstrating that benzene produces lymphomas in laboratory animals and that it produces genotoxicity in exposed humans. Accordingly, there seems to be little reason to question the conclusion that it is biologically plausible that benzene is a cause of human lymphatic tumors.

In recent years there has also been an increase in the reliance on mechanistic information in reaching conclusions about the chemical causation of cancer. This is evident in the criteria used by IARC and by NTP in classifying a chemical as a Group 1 or known human carcinogen. The epidemiological evidence no longer need be sufficient by itself for either the IARC or NTP hazard identification process, in both of which the highest level of concern, Group 1 or "known" can be achieved if the mechanistic evidence in humans is strong and consistent with an accepted mechanism of carcinogenesis. Based upon the evidence in humans supporting a biologically plausible mechanism of carcinogenesis, on the current understanding of the effects of benzene on early bone marrow stem cells, on the further recognition of the molecular biology of lymphomas, on the insights provided by the evolving classification of human lymphomas, and on the existing epidemiological data, benzene should be considered a cause of human lymphoproliferative disorders.

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Conflict of interest statement

I have served as an expert witness in toxic tort cases related to benzene, roughly equally for plaintiff and for defence. He has expressed expert opinions consistent with the interpretations in this paper.

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