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Review

Lymphohematopoietic cancers induced by chemicals and other agents and their implications for risk evaluation: An overview

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ABSTRACT

Lymphohematopoietic neoplasia are one of the most common types of cancer induced by therapeutic and environmental agents. Of the more than 100 human carcinogens identified by the International Agency for Research on Cancer, approximately 25% induce leukemias or lymphomas. The objective of this review is to provide an introduction into the origins and mechanisms underlying lymphohematopoietic cancers induced by xenobiotics in humans with an emphasis on acute myeloid leukemia, and discuss the implications of this information for risk assessment. Among the agents causing lymphohematopoietic cancers, a number of patterns were observed. Most physical and chemical leukemia-inducing agents such as the therapeutic alkylating agents, topoisomerase II inhibitors, and ionizing radiation induce mainly acute myeloid leukemia through DNA-damaging mechanisms that result in either gene or chromosomal mutations. In contrast, biological agents and a few immunosuppressive chemicals induce primarily lymphoid neoplasms through mechanisms that involve alterations in immune response. Among the environmental agents examined, benzene was clearly associated with acute myeloid leukemia in humans, with increasing but still limited evidence for an association with lymphoid neoplasms. Ethylene oxide and 1,3-butadiene were linked primarily to lymphoid cancers. Although the association between formaldehyde and leukemia remains controversial, several recent evaluations have indicated a potential link between formaldehyde and acute myeloid leukemia. The four environmental agents examined in detail were all genotoxic, inducing gene mutations, chromosomal alterations, and/or micronuclei *in vivo*. Although it is clear that rapid progress has been made in recent years in our understanding of leukemogenesis, many questions remain for future research regarding chemically induced leukemias and lymphomas, including the mechanisms by which the environmental agents reviewed here induce these diseases and the risks associated with exposures to such agents.

Contents

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1. Introduction to lymphohematopoietic cancers

Lymphohematopoietic neoplasia can be described as an uncontrolled proliferation or expansion of hematopoietic and lymphoid cells that are unable to differentiate normally to form mature blood cells [1]. These neoplasms represent clonal expansions of hematopoietic cells that occur almost always within either the myeloid or lymphoid lineage [2,3]. The myeloid clones are designated as chronic or acute leukemias, depending upon the rate of clonal expansion and the stage of differentiation that dominates the leukemic clone. Lymphoid neoplasms typically manifest themselves in the blood as chronic or acute lymphoblastic leukemias (ALLs) or remain confined to lymphoid proliferative sites such as the lymph nodes or spleen and are designated as lymphomas [2]. Acute leukemias tend to have a rapid onset with a predominance of immature cells whereas chronic leukemias have a more insidious onset and progress over a period of months or years to a blast or acute leukemic phase.

Using this basic classification, leukemias can be described as one of four major types—ALL, acute myeloid leukemia (AML), chronic lymphoblastic leukemia (CLL), and chronic myeloid leukemia (CML). Similarly, lymphomas are broadly classified as Hodgkin lymphomas or non-Hodgkin Lymphomas (NHL) depending upon the appearance of a specific cancer cell type, the Reed-Sternberg cell, which is found in Hodgkin lymphomas [4]. Within these larger groupings, there are numerous subtypes involving specific cells that have unique characteristics, origins, and increasingly recognized clinical significance. These subtypes are generally classified according to morphologic, cytogenetic, immunophenotypic, and more recently, molecular characteristics according to the French-American-British (FAB) or World Health Organization (WHO) classification systems [3,5–7]. The more recent WHO classification system is a detailed and comprehensive classification scheme describing over 125 different lymphohematopoietic diseases with a focus on the origin of the neoplastic cell. While valuable for understanding specific disease subtypes, in practice, the WHO system is difficult to use in a overview article such as this and particularly when referring to leukemias and lymphomas in the older literature which were classified using earlier classification schemes. For simplicity, we have used the FAB classification, a less complicated system based on cell morphology that was commonly used in the past and is still widely used.

Among the leukemias, the two major diagnostic categories, ALL and AML, can be further classified based upon cellular features. ALL is subdivided by FAB morphology (L1, L2, and L3) and by immunophenotype (B-cell, early pre-B, pre-B, and T-cell) [8]. AML is classified primarily by morphological characteristics into eight different FAB subgroups (M0–M7) based upon the myeloid lineage and degree of maturation involved. Similarly, the myelodysplastic syndromes (MDSs), a series of blood disorders characterized by maturation defects resulting in ineffective hematopoiesis, have also been classified by the FAB and WHO systems. These are commonly considered to be preleukemic because significant proportion (up to 33%) of the various disorders progress to frank AML [3,6,9,10]. MDS developing in patients that have previously been treated with antineoplastic drugs or radiation (t-MDS) represents an early stage neoplasm and is now combined with therapy-related AML (t-AML) in the most recent WHO classification scheme [3].

The objective of this article is to provide an overview of the types of lymphohematopoietic neoplasia induced by chemical agents and radiation in humans, and to summarize recent information on the mechanisms of chemical leukemogenesis. Much of the discussion focuses on AML due to the limited and evolving knowledge about chemically induced lymphoid leukemias and lymphomas that is only now being integrated into ongoing epidemiological and clinical studies. An overview of the major classes of leukemia-inducing agents—radiation, the alkylating agents, and topoisomerase II inhibitors as well as some common environmental and occupational chemicals—is presented followed by a short discussion of factors influencing chemical leukemogenesis. Finally, the review concludes with a brief discussion of how mechanistic information on human leukemia-inducing agents may be used to inform risk evaluation from exposure to environmental agents.

2. Overall incidence and trends

Lymphohematopoietic neoplasms are an uncommon, yet significant, cause of cancer-related deaths. In 2013, it is estimated that leukemia will be diagnosed in 48,610 people in the United States [11]. About 44% of these will be chronic leukemias (21,600) with the remainder being acute leukemias (20,660) and others that are otherwise classified (6350). Because of the limitations of current therapies, leukemia represents the 6th leading cause of cancer deaths among males and females in the United States [11]. Furthermore, it is estimated that 79,030 new cases of lymphoma would be diagnosed in the United States in 2013 [11]. Of these, 89% were projected to be NHL and 11% Hodgkin lymphoma. Of those with lymphoma, approximately 20,000 are expected to die during 2013. Consequently, NHL represents the 7th leading cause of cancer-related deaths in females and the 9th in males. Incidence rates were stable in men and women for both non-Hodgkin and Hodgkin lymphoma from 2004 to 2008, whereas death rates for