Regulatory Toxicology and Pharmacology 55 (2009) 340–352

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

A hospital-based case-control study of acute myeloid leukemia in Shanghai: Analysis of personal characteristics, lifestyle and environmental risk factors by subtypes of the WHO classification

Otto Wong [a,b,c,*], Fran Harris [a,d], Wang Yiying [c], Fu Hua [c]

[a] Applied Health Sciences, San Mateo, CA 94401, USA
[b] University of Hong Kong, Hong Kong, China
[c] Fudan University School of Public Health, Shanghai, China
[d] University of California School of Medicine, San Francisco, CA, USA

ARTICLE INFO

Article history:
Received 8 July 2009
Available online 22 August 2009

Keywords:
Acute myeloid leukemia
AML
AML subtypes
World Health Organization classification
Epidemiology
Case-control study
Risk factors
Environment
Shanghai
China

ABSTRACT

Objectives: The objectives are (1) to investigate and identify potential risk factors (personal characteristics, lifestyle and environmental factors) of acute myeloid leukemia (AML), and (2) to explore the relationships between potential risk factors and AML subtypes according to the World Health Organization (WHO) classification of myeloid neoplasms.
Materials and methods: The investigation was a hospital-based case-control study consisting of 722 confirmed AML cases and 1444 individually gender-age-matched patient controls at 29 hospitals in Shanghai. A 17-page questionnaire was used to obtain information on: demographics, medical history, family history, lifestyle risk factors, employment history, residential history, and environmental and occupational exposures. Certain occupations of interest triggered a second questionnaire, which was occupation-specific and asked for more details about jobs, tasks, materials used and work environment. Risk estimates (odds ratios and 95% confidence intervals) were calculated using conditional logistic regression models.
Results: Several potential risk factors of AML (all subtypes combined) and individual subtypes were identified; including low-level education, body mass index (BMI), blood transfusion, smoking, alcohol consumption, home or workplace renovation, living on a farm, planting crops, raising livestock or animals, employment as farm workers or in the agricultural industry, and exposures to insecticides or fertilizers. Some risk factors applied to all or several subtypes (such as low-level education and living on a farm), while others were limited to one or two specific subtypes (such as home/office renovation and acute promyelocytic leukemia). An inverse association was found between BMI and overall AML or the sub-category "AML not otherwise categorized", whereas a positive association between BMI and the subtype acute promyelocytic leukemia was detected. An unexpected finding was the association between the use of traditional Chinese medicines and a reduced risk of AML in general as well as several major subtypes.
Conclusions: The study identified a number of risk factors for AML in general as well as for some specific subtypes. Some of the risk factors were subtype-specific. The difference in risk by subtype underscores the importance of investigating the etiologic commonality and heterogeneity of AML by subtype in epidemiologic research.

1. Introduction

Acute myeloid leukemia (AML) is the most common type of leukemias in the United States and other western countries. The estimated number of newly diagnosed AML in the US for 2008 was 13,290, with a male-to-female ratio of 1.2:1.0 (Jemal et al., 2008). Based on the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) data for 2001–2005, the adjusted annual incidence rates for males and females were 4.5 per 100,000 and 2.9 per 100,000, respectively (Reis et al., 2008). There are some variations in incidence by ethnicity and geographical location. For example, in the US the rates for males and females classified as "Asian/Pacific Islanders" are 3.7 per 100,000 and 2.5 per 100,000, respectively, which are slightly lower than those for their white counterparts (4.6 per 100,000 and 3.0 per 100,000). Generally, the incidence of AML in adults is higher in developed countries

* Corresponding author. Address: Applied Health Sciences, San Mateo, CA 94401, USA.
E-mail address: ottowong@aol.com (O. Wong).

0273-2300/$ - see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.yrtph.2009.08.007

than in less developed nations. Incidence rates of AML in Asian countries such as China and Japan are generally lower than those in the US and European nations (Linet and Cartwright, 1996).

Most early epidemiologic studies treated leukemia as a single diagnostic category, partly because of the lack of specific diagnostic information and partly because of the limited number of patients by subgroups of leukemia in individual studies. However, starting in the 1980s, following the clinical and pathological recognition of the heterogeneity of leukemias, epidemiologists began to appreciate the differences among the various subgroups within the broad category of malignancies collectively known as "leukemia", and an increasing number of investigations focusing on specific major subgroups of leukemia (acute and chronic myeloid leukemias, and acute and chronic lymphocytic leukemias) began to appear in the literature (Linet, 1985). A previous comprehensive review has identified a large number of potential risk factors of AML reported in epidemiologic investigations; including personal and family medical histories (such as blood transfusion, alkylating drugs for cancer treatment, diagnostic X-rays, rheumatoid arthritis, and family history of blood disorders), lifestyle (such as tobacco, alcohol, and hair dyes), environmental exposures (living on a farm, living near electrical power transmission lines), occupations and industries (such as farmers, painters, shoe and leather workers, chemical workers, printers, and grain workers), and exposures to chemical, physical or biological agents (such as benzene, solvents, radiation, and retroviruses) (Linet and Cartwright, 1996). In addition, some recent studies have reported a positive association between anthropometric measurements (such as weight, height or body mass index) and lymphatic and hematopoietic malignancies including AML (Larsson and Wolk, 2008; Engeland et al., 2007; Kasim et al., 2005; Ross et al., 2004).

The findings of AML risk factors reported in epidemiologic studies, however, have not always been consistent. For example, while epidemiologic evidence generally suggests an increased risk of AML among smokers, no association between cigarette smoking and AML was found in some case-control studies (Flodin et al., 1986; Kabat et al., 1988; Spitz et al., 1990). Other studies have reported that cigarette smoking seems to affect certain subtypes of AML more than the others (Pogoda et al., 2002; Moorman et al., 2002). This observation of difference in risk by subtype underscores the fact that the diagnostic category of AML actually consists of several distinct subtypes and, hence, the need for epidemiologic studies of AML to treat these subtypes as separate diagnostic entities (Linet and Cartwright, 1996). A new classification of myeloid neoplasms was introduced by the World Health Organization (WHO) in 2001 (Jaffe et al., 2001; Vardiman et al., 2002). At the present, there are no epidemiologic studies that systematically investigate the effects of personal, lifestyle, and environmental risks of individual AML subtypes based on the WHO 2001 classification. Epidemiologic studies to investigate the etiologic commonality and heterogeneity of AML subtypes using the new WHO classification are needed.

The objectives of the present study are twofold: (1) to investigate and identify potential risk factors (including personal characteristics, lifestyle, environmental factors, occupations, industries, and specific exposures) of AML in Shanghai, and (2) to explore the relationships between potential risk factors and specific AML subtypes according to the new WHO classification of myeloid neoplasms. In this report, we will present results based on an analysis of personal characteristics, lifestyle and environmental risk factors. Detailed analysis of occupations and specific exposures will be reported separately in the future.

2. Materials and methods

We conducted a hospital-based case-control study of AML in Shanghai. The study was one of several parallel but independent research projects of the Shanghai Health Study (SHS) program, a collaborative research effort between investigators in the US and China. Participants of and contributors to the SHS program included both Chinese and US organizations: Fudan University, Shanghai Center for Disease Control and Prevention (CDCP), Shanghai Municipal Institute of Public Health Supervision (IPHS), Shanghai District Institutes of Public Health Supervision, University of Colorado, Applied Health Sciences, ExxonMobil Biomedical Sciences, and 29 hospitals in Shanghai. A pilot study was carried out in 2001–2002 to assess the feasibility of the program. Study protocols and data collection instruments (such as questionnaires) of individual research projects as well as the overall SHS program organization were developed in 2002–2003. The study protocols were approved by Chinese and US Institutional Review Boards of respective organizations.

In designing the study, it was estimated that a sample size of approximately 500–600 AML patients would provide adequate statistical power to detect a modest risk of AML resulting from benzene exposure (one of the chemicals of primary interest). It should be noted that even though benzene was of primary interest in any investigation of AML including ours, other risk factors (personal, lifestyle, environmental and occupational) were also taken into consideration in the study protocol as reflected in the design of the questionnaire. Thus, the sample size was adequate to detect a modest risk for other factors that were as frequent as benzene exposure in the target population. Based on crude hospital admission data in Shanghai, it was anticipated the targeted sample size could be reached in 4–5 years.

For the AML case-control study, cases were defined as patients aged 18 or older and diagnosed with AML ("provisional diagnosis") at any of the 29 participating hospitals in Shanghai between August 2003 and June 2007. The WHO 2001 classification of AML was used in the diagnosis (Jaffe et al., 2001). The WHO classification system utilizes not only morphologic findings but also genetic, immunophenotypic, biologic, and clinical features of the patients (Vardiman et al., 2002). To provide the equipment and facilities needed for the WHO diagnostic procedures, a new laboratory "the Joint Sino-US Clinical and Molecular Laboratory (JCML)" was built on the campus of Fudan University in Shanghai, staffed with scientists from both Fudan University and the University of Colorado. The JCML functioned as the centralized diagnostic laboratory for the participating hospitals in Shanghai and served as the clinical arm to provide diagnostic information to the research projects in the SHS program.

At each participating hospital, a designated clinical coordinator was responsible for identifying and recruiting eligible patients (i.e., patients with a provisional diagnosis of AML and aged 18 or older) for study participation. Each participant was asked to sign an informed consent according to the Declaration of Helsinki of 1975. Peripheral blood, bone marrow aspirates, tissue and core biopsies were collected in conjunction with diagnostic procedures and were sent to JCML for analysis. Details of diagnostic procedures at JCML have been described elsewhere (Bao et al., 2006; Gross et al., 2008). The clinical coordinators at the participating hospitals were also responsible for recruiting controls. For each case, two individually matched controls were randomly selected from patients admitted to the same hospital. Patients with any malignant or non-malignant diseases of the lymphatic and hematopoietic system were excluded from control selection. Matching criteria included gender and age. For each case, the clinical coordinators at the hospitals were asked to recruit two patients of the same gender within 5 years of age of the case. For some cases, suitable controls within 5 years of age were not available and the age requirement was relaxed. Because cases and controls were enrolled around the same time, hospital admission dates of the case and controls within each matched set (matched triplet) were quite similar.