benzene exposure lead to the pattern of sAML observed following alkylation therapy or can benzene exposure also result in AML developing as a consequence of balanced translocations, such as those frequently encountered in primary AML or those observed following treatment with Topoisomerase II inhibitors? Is AML developing secondary to benzene exposure a high dose phenomenon or can it occur at relatively low concentrations? Is there a sharp discontinuity in the dose-response curve as suggested in recent studies employing cumulative exposure as a metric [50;51;82]? Is the dose-response different for individual diseases, i.e. AA, MDS or AML? Can benzene-induced AML present in the absence of previous evidence of blood dyscrasias or sMDS, or is it virtually always a consequence of a progression from clinically significant bone marrow suppression to sMDS to sAML? Are there differences in the clinical presentation, response to treatment and risk of transformation to sAML between cases of idiopathic acquired AA and AA developing as a result of benzene exposure? Nearly all of these questions have a significant impact on determining prognosis for patient counseling and for future benzene risk assessment.

2.5 Research Design

The over-arching study design will be a case control study for: AA, AML and MDS (case-control comparisons for AML will also be provided in an independent NHL/AML case control study). This design is necessary to compare benzene dose-response for individual disease entities. In addition, case series descriptions and a comparison of selected parameters and disease progression will be conducted for AA, MDS and AML. Controls for the case-control study will be matched individuals presenting with non-lympho-hematopoietic cancer and controls for the case series will be cases of the same disease that are not likely to be due to benzene exposure (See section 8.1). Hematopoietic diseases with known heritable or nutritional etiology are specifically excluded (See section 8.B).

A Identification of the Study Populations and Enrollment of Subjects

Cases will be ascertained from five different sources, which will encompass various cases of disease severity. The five sources will consist of: (a) inpatients presenting at 30 primary and tertiary referral hospitals in Shanghai, (b) outpatients with mild disease presenting at district central hospitals in Shanghai, (c) cases of BP referred by rural workplace clinics, hospitals and physicians outside of the Shanghai metropolitan area, and (d) surviving cases of BP reported in the SMCDCP database since 1986. In addition, any cases of BP not identified through the above sources, but present in a companion molecular epidemiology study are also be eligible for recruitment as cases. The recruitment period for hematopoietic diseases will extend through June, 2007 and for lymphoid neoplasms through December, 2007. Specific clinical criteria for ascertainment of cases from these individual sources are outlined in the Research Protocol.

A.1 Inclusion Criteria

a Any individuals 18-75 years of age presenting at participating referral hospitals with any combination of signs or symptoms consistent with severe AA, MDS or AML are potential subjects for this study.