Chronic Lymphocytic Leukemia: Reconsideration of Exclusion from Eligibility for Compensation under EEOICPA

Available scientific evidence does not provide sufficient grounds for continuing to regard chronic lymphocytic leukemia (CLL) as a non-radiogenic form of cancer.

Biological Basis for Radiation-Induced CLL

Contemporary understanding of radiation carcinogenesis is grounded in our understanding of the physical processes by which ionizing radiation influences neoplastic transformation at a molecular level. While epidemiological findings contribute to the scientific literature on radiation carcinogenesis, particularly risk assessments, conclusions regarding ionizing radiation as a cause of human cancer are based upon a synthesis of evidence from molecular and cytogenetic research, experimental studies in radiobiology, epidemiology, and theoretical work on cancer causation. To date, NIOSH appears to have given a relatively small amount of weight to the evidence regarding the mechanistic understanding of radiation carcinogenesis as it applies to CLL pathogenesis, while giving a relatively large amount of weight to evidence from observational (i.e., non-randomized) epidemiological research in which analyses are susceptible to biases from selection, confounding, and measurement error. This is an inappropriate weighting of evidence for the evaluation of whether ionizing radiation exposure is a cause of CLL. Evidence derived from research in fields other than epidemiology is important to an evaluation of whether ionizing radiation is a cause of CLL, particularly given the limitations of the epidemiologic literature on this topic.

Somatic mutations (along with functional aberrations in immune function) appear to play a central role of in the pathogenesis of CLL (Stevenson et al. 1998; Magrath 1992). Chromosomal abnormalities are detected in the majority of CLL cases (Stilgenbauer et al. 2002). The type of mutations observed in clonal cells obtained from CLL patients, primarily deletions of chromosomal material, require double strand breaks of the chromosomal DNA in order to occur (Dewald et al. 2003; Stilgenbauer et al. 2000). The conclusion that these somatic mutations play a causal role in the etiology of CLL is strengthened by the observation that two tumor suppressor genes that are inactivated as a result of common CLL mutations, *p53* and *ATM*, are established causal contributors to malignant transformation.

It is well-established that ionizing radiation has the ability to produce double strand breaks in chromosomal DNA (United Nations Scientific Committee on the Effects of Atomic Radiation 2000). Therefore, ionizing radiation exposure could play a role in one or more stages of the multi-stage process of neoplastic transformation that leads to CLL. Further, it is plausible that some early stage mutational events may increase the likelihood of ionizing radiation exposure influencing later stage transformations. For example, in a considerable proportion of CLL clones (approximately 20%) the *ATM* gene is mutated; the *ATM* gene product is known to be involved in the repair of DNA double strand breaks (Dunst et al. 1998; Humphreys et al. 1989; Jones et al. 1995; Parshad et al.

1985; Stilgenbauer et al. 2000) and mutations of this gene are associated with increased vulnerability to the carcinogenic effects of ionizing radiation.

In summary, CLL is similar to other hematological malignancies whose pathogenesis involves mutational changes at the molecular level that ultimately lead to malignant transformation of a cell (Irons and Stillman 1996). Ionizing radiation has the ability to produce mutations, including double strand breaks in chromosomal DNA. This evidence regarding the molecular basis of CLL induction should contribute substantial weight to a scientific evaluation of the question of whether ionizing radiation is a cause of CLL, with this literature supporting the conclusion that ionizing radiation exposure can produce the somatic mutations that contribute to the pathogenesis of CLL.

Limitations of Epidemiologic Evidence

The primary reason that NIOSH has given for exclusion of CLL from coverage under EEOICPA is that there is minimal epidemiological evidence supporting the conclusion that ionizing radiation exposure increases CLL risk. However, when evaluating epidemiological findings it is important to recognize that some health outcomes are more difficult to study with epidemiological methods than other health outcomes. In general, rare diseases are more difficult to study than more common outcomes, because study findings tend to be limited by low statistical power. Diseases that occur promptly after exposure tend to easy to study in association with the exposure than diseases that have protracted induction and latency periods; and, diseases that are highly fatal tend to be easier to study than diseases that less fatal, since epidemiologists often rely upon cause of death information. These are important considerations for understanding the limitations of the epidemiological literature on CLL-radiation exposure associations.

Most studies in the epidemiological literature on CLL among radiation-exposed populations include small numbers of CLL cases, and therefore provide results that suffer substantial statistical uncertainty.

Many of these investigations fail to appropriately account for a protracted induction, latency, and morbidity period between radiation exposure and CLL mortality. Analytically, in order for an investigation of radiation-induced CLL mortality to detect an effect, the study must encompass a period of follow-up that is long enough to allow for an extended induction, latency and morbidity period after exposure occurs. Studies with short duration of follow-up (e.g., 1 or 2 decades) could observe no effect of ionizing radiation on CLL simply because the time from exposure to end of follow-up is less than the minimal induction, latency, and morbidity period for radiation-induced CLL mortality. Furthermore, the ability to detect an association, if one exists, requires relating CLL incidence or mortality to exposures in the distant past using appropriate methods of survival analysis. If the effect of radiation on CLL risk only becomes apparent many years (or a few decades) after irradiation, then analyses conducted under relatively short exposure lag assumptions may suffer serious exposure misclassification problems. Nonetheless, many of the published studies have given minimal attention to evaluation of protracted induction/latency periods in radiation-CLL analyses.

Patients diagnosed with CLL often live many years without developing evidence of significant symptoms, and many patients die with the disease, but from causes other than CLL (Crespo et al. 2003). Consequently, CLL is not necessarily the underlying cause of death recorded on a death certificate, and in fact, may not be indicated on the death certificate at all. Furthermore, the direct repercussions or complications of CLL are often non-specific, including immunodeficiency, and may increase the likelihood of infectious or malignant disease, thereby increasing the opportunity for conditions other than CLL to be recorded as the underlying cause of death. Therefore, case ascertainment may be poor and partly obscured by competing causes of death.

Consequently, the epidemiological literature on radiation-CLL associations is characterized by studies that have tended to very limited ability to detect associations between radiation exposure and CLL.

CLL among Japanese A-bomb survivors

NIOSH has noted that "no elevation of CLL incidence had been observed among Japanese A-bomb survivors" in the Life Span Study (LSS). However, for evaluation of CLL risk following exposure to ionizing radiation, the LSS provides minimal information because the incidence of CLL is extremely low in Asian populations (Finch and Linet 1992; Groves et al. 1995). For example, in analyses of cancer incidence during the period 1950-1987 among 86,293 A-bomb survivors in the LSS cohort, only 4 CLL cases were included. Given the small number of CLL cases, specific analyses of radiation-CLL associations have not been reported (Preston et al. 1994; Tomonaga et al. 1993).

Much of the research published over the past 50 years on the effects of the atomic bomb on CLL incidence and mortality in the LSS suffered problems of case misclassification (Preston et al. 1994). Following an extensive review of hematological specimens for leukemia cases identified during the period from 1945 through 1980 it was determined that 7 of the 10 CLL cases registered during that period were, in fact, not CLL. These were determined to be cases of acute T-cell leukemia (ATL), a relatively common disease among Nagasaki residents regardless of their status as an A-bomb survivor. Consequently, reports on radiation-CLL associations that are based on information collected prior to this reclassification of leukemia are of questionable reliability due to these problems of case misclassification.

CLL among workers in the nuclear industry

The epidemiological literature on cancer mortality among workers in the nuclear industry provides minimal basis for evaluating the effects of external exposure to ionizing radiation on CLL due to low statistical power. Among the largest of these occupational cohort studies pertains to analyses that combined mortality information on 95,673 nuclear industry workers in the United States, United Kingdom, and Canada (average cumulative dose was 40 mSv). A negative association between ionizing radiation exposure under a 2-year exposure lag assumption and CLL mortality was observed (excess RR per Sv=-0.95, 90%CI: -4.0, 9.4).

However, it stretches the practical limits of epidemiology to expect to directly estimate risk from occupational cohort data in which few cases are observed in the higher (e.g., >=100 mSv) dose range; of the 27 CLL cases observed in the international collaborative study of nuclear workers, only 1 case was observed among workers who had >=100 mSv cumulative dose (Cardis 1995). Furthermore, under a reasonable exposure lag assumption for a slow-progressing disease like CLL (e.g., 20 years), the distribution of CLL cases with respect to cumulative radiation dose would tend to shift further towards zero. Such considerations underline the limited power of nuclear worker cohort studies to derive radiation risk estimates for CLL mortality.

CLL among other radiation-exposed populations

Among the studies of other radiation-exposed populations, of particular importance, given the size of the study cohort, duration of follow-up, and average magnitude of radiation dose, are the results of a study of cancer mortality among approximately 14,000 British ankylosing spondylitis patients who were treated by x-irradiation between 1935 and 1954 (average bone marrow dose estimated as 4400 mSv). With vital status follow-up through 1991, it was found that these patients were more likely to have a death attributed to CLL than members of the general population (observed=7, SMR=1.44, 95% CI: 0.6, 2.8) (Weiss et al. 1995). Furthermore, consistent with expectations of long latency and morbidity periods for CLL mortality, excess CLL mortality was observed almost exclusively in the period 25+ years after irradiation (in contrast to acute and myeloid leukemia, for which a peak in excess mortality was observed in the first five years post-treatment). Under a 25-year exposure lag assumption, a two-fold excess of CLL mortality was observed (observed=6, SMR=1.97, 95%: CI 0.7, 4.3) (Weiss et al. 1994).

The incidence of CLL was examined in a cohort of 20,204 Swedish patients who were treated by radiotherapy between 1950-1964 for benign diseases of the locomotor system such as ankylosing spondylitis, arthrosis, and spondylosis (average bone marrow dose estimated as 400 mSv) (Damber et al. 1995). In comparison to the British ankylosing spondylitis patients, the radiation doses delivered to these patients were typically an order of magnitude lower and only small parts of the body were irradiated (Damber et al. 1995). Patients were classified into three groups based on estimated radiation doses (<0.20, 0.20-0.50, and >0.50 Gy); and, standardized incidence ratios (SIRs) were calculated under a 0-year exposure lag assumption (there was no evaluation of variation in cancer risk with time since irradiation). There was a slight deficit of CLL among patients who received the lowest radiation doses (observed=19, SIR=0.94, 95%CI: 0.6, 1.5) and a small excess of CLL among patients in the upper two dose groups (observed=15, SIR=1.17, 95% CI: 0.7, 1.9 and observed=16, SIR=1.18, 95% CI: 0.7, 1.9, respectively).

Among 12,955 female patients who were treated by radiotherapy for benign gynecological disorders (median dose to active bone marrow estimated as 1200 mSv), CLL mortality rates (pooled together with lymphatic leukemia not otherwise specified, LL) were elevated when compared to general population mortality rates (observed=17, SMR=1.8, 95%CI: 1.0, 2.9) (Inskip et al. 1993). Consistent with expectations of a

protracted latency and morbidity period, there was no excess of CLL mortality in the first 10 years of follow-up (observed=1, SMR=0.93, 95% CI: 0.0, 5.2). In subsequent decades after irradiation, however, there was an excess of CLL mortality among irradiated patients. Under 20 and 30-year exposure lag assumptions, the ratios of observed to expected CLL deaths were 1.64 (observed=10, 95% CI: 0.8, 3.0) and 2.2 (observed=7, 95% CI: 0.9, 4.5), respectively. A comparison was also drawn using an internal referent population (a group of 3185 patients with treatments other than radiotherapy). Comparisons between irradiated and non-irradiated patients by leukemia sub-type produced highly unstable results due to the small number of leukemia cases in the non-irradiated group. The overall rate ratio for CLL comparing irradiated to non-irradiated patients was 1.1 (90%CI: 0.5, 3.0); under 20- and 30-year exposure lag assumptions, the rate ratios for CLL comparing irradiated to non-irradiated patients were 1.3 and 2.3, respectively.

Investigations of CLL mortality among women treated by radiotherapy for excessive uterine bleeding (metropathia hemorrhagica) (Darby et al. 1994) and women treated by radiotherapy for infertility or amenorrhea (Ron et al. 1994a) have not reported on the risk of CLL following irradiation due to the small numbers of CLL cases (1 and 2 CLL deaths, respectively) observed in these cohorts.

In a cohort study of second cancers following radiotherapy for invasive cancer of the uterine cervix among 182,040 women (average bone marrow dose was estimated as 7100 mSv), the observed and expected number of second cancers were examined (Boice et al. 1985). In the first decade after irradiation there were fewer than expected cases of CLL (observed=9, O/E=0.7, 95% CI: 0.3, 1.3), while under a 20-year exposure lag assumption a small excess of CLL mortality was reported (observed=3, O/E=1.25, 95% CI: 0.3, 3.7). A case-control study of secondary cancers following radiotherapy for invasive cancer of the uterine cervix was conducted building upon this cohort analysis (Boice et al. 1987). The study included leukemia cases that were diagnosed at least 1 year after diagnosis of cervical cancer with four controls matched to each case. CLL incidence among patients treated by radiotherapy was compared to CLL incidence among patients treated by other means. No excess of CLL was observed when comparing patients treated by radiotherapy to other patients (RR=1.03, 90% CI: 0.3, 3.9). Reported results pertain to a 1-year exposure lag assumption.

In case-control studies of leukemia following radiotherapy for invasive cancer of the uterine corpus (Curtis et al. 1994) and breast cancer (Curtis et al. 1989), leukemia cases were identified between 1935 and 1985 using cancer registry data and controls were matched by cancer registry, age and year of diagnosis, and race. Among patients treated for cancer of the uterine corpus, the RR for CLL comparing patients treated by radiotherapy to others was 0.90 (95% CI 0.4, 1.9). Among patients treated by radiotherapy for breast cancer, the RR for CLL comparing patients treated by radiotherapy to others was 1.84 (95% CI 0.5, 6.7). Neither of these studies reported on evaluation of variation in the association between CLL and radiotherapy treatment with time-since-treatment.

Summary and Conclusions

NIOSH commented that "NIOSH does not assert that evidence proves CLL is non-radiogenic, only that the weight of evidence has not supported the case for radiogenicity." In fact, the scientific evidence pertaining to the molecular mechanisms of CLL induction weighs heavily towards the conclusion that CLL is similar to other hematological malignancies whose etiology involves structural changes on the chromosomal level that cause mutational changes on the molecular level, altering important cellular functions, and, ultimately, leading to malignant transformation of a cell. The weight of this scientific evidence is in support of the conclusion that the somatic mutations that contribute to the genesis of CLL can be produced by ionizing radiation exposure.

As NIOSH has noted, epidemiological studies of cancer among A-bomb survivors provide little basis for determination of whether radiation exposure is a cause of CLL. Recent analyses of cancer incidence over the period 1950-1987 include only 4 CLL cases; given the small number of CLL cases, specific analyses of radiation-CLL associations have not been reported (Preston et al. 1994; Tomonaga et al. 1993). NIOSH has compiled a bibliography of epidemiological literature related to the topic of CLL radiogenicity. This bibliography includes a large number of occupational cohort studies; as noted above, findings derived from occupational cohort studies are characterized by extremely low statistical power to address the question of whether radiation exposure causes CLL. Of less direct relevance to the EEOICPA than occupational cohort studies are studies that examine CLL following medical irradiation. Analyses of British ankylosing spondylitis patients treated by radiotherapy cannot be taken as persuasive evidence against radiation-effects on CLL mortality. In fact, there is a 44% excess of CLL mortality among ankylosing spondylitis patients compared to the general population. The fact that CLL deaths occurred much later than the deaths due to acute and myeloid leukemias may reflect the typically prolonged latency and morbidity period for CLL cases. Studies of patients treated for benign gynecological disease cannot be taken as persuasive evidence that CLL is non-radiogenic. Inskip et al. report an 80% excess of CLL mortality among patients treated by radiotherapy for benign gynecological disorders compared to the general population. Internal comparisons of CLL among irradiated and non-irradiated patients resulted in a very small estimate of CLL risk bounded by wide confidence intervals reflecting the small size of the non-irradiated comparison group. The difference in CLL mortality between irradiated and non-irradiated patients was of largest magnitude for the period 30+ years post-irradiation. While the internal referent group was extremely small, and consequently these results are highly imprecise, this pattern is consistent with expectations of an extended induction, latency and morbidity periods. Studies of radiotherapy treatment for malignant disease (cervical, uterine, and breast cancer) suggest that CLL is not associated with high dose radiotherapy. However, there are significant limitations to these studies. The most notable of these is the absence of evaluation of variation in radiation-CLL risk with time-since-exposure. In addition overmatching could have forced comparability of exposure status between cases and controls (thereby minimizing ability to detect the effect of radiotherapy treatment). Further, in studies of patients irradiated as treatment for a previous cancer the radiation doses delivered tend to be extremely high and localized

with the intended effect of cell killing in the irradiated area, which effectively prevents cancer induction and may attenuate any evidence of a dose-response relationship; and, patients being treated for an existing cancer may receive chemotherapy in conjunction with radiotherapy that may influence subsequent cancer incidence. The epidemiologic evidence regarding the radiogenicity of CLL is relatively weak; it should not be given a disproportionate weight (relative to evidence from other scientific disciplines) when drawing conclusions regarding whether ionizing radiation is a cause of CLL. Given the limitations of the reviewed epidemiologic studies, these findings do not offer a persuasive basis for concluding that CLL is an exception to general principles of radiation carcinogenesis.

NIOSH has noted the inconsistency of classifying as eligible for compensation all sub-types of lymphatic malignancies other CLL, despite the similarities shared by some of these diseases. For example, the Revised European American Lymphoma classification scheme, which is widely accepted and was adopted by the World Health Organization, considers B-cell CLL and small lymphocytic lymphoma (SLL, a sub-type of non-Hodgkin's lymphoma) to be a single disease entity, in recognition of the biological and clinical similarities between these B-lymphocyte malignancies (Harris et al. 1999). Consequently, there is a problem of logical inconsistency if the EEOICPA continues to assert that CLL is non-radiogenic while SLL is radiogenic. Contemporary classification schemes hold that B-cell CLL and SLL are a single disease entity.

Conclusion

Available scientific evidence suggests that CLL incidence will be increased by exposure to ionizing radiation. Scientific evidence does not provide a sufficient basis for regarding CLL as non-radiogenic.

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