Review of the report "Development of a CLL Risk Model for NIOSH-IREP" by John R. Trabalka and A. Iulian Apostoaei. Draft dated December 21, 2007; amended January 30, 2009 (reformatted June 30, 2009).

Overview

The lymphomas (Hodgkin's lymphoma and non-Hodgkin's lymphoma) and multiple myeloma are considered together in NIOSH-IREP, using the Radiation Effects Research Foundation (RERF) incidence data for 1950-1987 for the Japanese atomic bomb survivors, as reported by Preston *et al.* (1994). Thus, the data upon which the current NIOSH-IREP lymphoma-multiple myeloma model is based was published 15 years ago. The incidence data for solid tumours among the Japanese atomic bomb survivors has recently been updated by Preston *et al.* (2007), covering the period 1958-1998, and an update of the incidence data for lymphatic and haematopoietic cancers (i.e. cancers other than solid tumours) is expected soon. It may be prudent to enquire of RERF as to when this latter update might be expected to be published since

- It would be of value to know what impact (if any) the recent lymphoma and multiple myeloma incidence data for the Japanese atomic bomb survivors have upon the current NIOSH-IREP lymphoma-multiple myeloma risk model, and

- It would be of value to know whether the recent incidence data for haematopoietic cancers shed any light upon the risk of chronic lymphocytic leukaemia (CLL) among the Japanese atomic bomb survivors

Should publication of the RERF update of lymphatic and haematopoietic cancers incidence among the Japanese atomic bomb survivors be within an acceptable timescale, it may be advisable to await these latest findings before making any decisions about CLL and the applicability of the current lymphoma-multiple myeloma risk model. This is particularly so if radiation-induced lymphatic and haematopoietic cancers other than the acute leukaemias and chronic myeloid leukaemia have characteristically long latent periods (as discussed by Trabalka and Apostoaei). Further, the authors from the RERF published risk models in their update of solid tumours incidence among the Japanese atomic bomb survivors, and these models were somewhat different from, for example, those published in the BEIR VII Report (2006). Again, it might be advisable to assess what the RERF researchers have to say about relevant risk models for lymphatic and haematopoietic cancers before finalising any model for CLL. However, since CLL is rare among the Japanese population it may well be that the next update of the incidence of CLL among the Japanese atomic bomb survivors will not add significantly to the information currently available. Nonetheless, the additional information on the lymphomas and multiple myeloma could indirectly illuminate the question of how to deal with CLL.

It would seem to be the case that chronic lymphocytic leukaemia (CLL) is more akin to a lymphoma (specifically, non-Hodgkin's lymphoma) than to an acute leukaemia or chronic myeloid leukaemia. Since NIOSH-IREP has a risk model for the lymphomas and multiple myeloma – in fact, just one risk model covering all the lymphatic and haematopoietic cancers other than the leukaemias – then it is arguable that CLL should be included in the NIOSH-IREP programme, since CLL is the only malignant neoplastic disease currently omitted from this programme. The evidence for CLL being capable of induction by ionising radiation is weak. However, the evidence for ionising radiation increasing the subsequent risk of lymphoma/multiple myeloma, particularly Hodgkin's lymphoma, cannot be considered strong, and it is not obvious that these cancers should be considered capable of induction through exposure to ionising radiation and therefore included in a radiation worker compensation program – the UK Compensation Scheme for Radiation-linked

Diseases, for example, does not consider Hodgkin's lymphoma to be sensitive to induction by radiation. However, if the lymphomas and multiple myeloma, particularly Hodgkin's lymphoma, are included among the cancers that are compensatable in the NIOSH-IREP programme then it is reasonable that CLL should be evaluated for inclusion, even in the absence of persuasive evidence of radiation-induction. Had EEOICPA excluded cancers such as Hodgkin's lymphoma (as in the UK Compensation Scheme) for which the evidence for radiation induction is also weak then the position with respect to CLL would be a different matter, but it is only CLL that is currently excluded.

The NRRW-3 Study

The third analysis of data from the UK National Registry for Radiation Workers (NRRW) was published earlier this year (Muirhead *et al.*, 2009). This is the most statistically powerful study of radiation workers to be published to date, and is of particular relevance to the circumstances of radiation workers in the USA. The authors found no evidence of an association between CLL and radiation exposure, even with a 10-year lag – the trends of CLL mortality and incidence with cumulative radiation dose were negative (but were not statistically significant). Muirhead *et al.* also reported positive trends with dose for non-Hodgkin's lymphoma and multiple myeloma mortality and incidence, and negative trends with dose for Hodgkin's lymphoma mortality and incidence – the positive trend with dose for multiple myeloma incidence was statistically significant, but the other trends were not statistically significant.

So, the NRRW-3 study does not support CLL being capable of induction by ionising radiation (although results for lags greater than 10 years are not reported); but then the study also does not support Hodgkin's lymphoma being capable of induction by ionising radiation and this cancer is included as compensatable in the NIOSH-IREP programme. The NRRW-3 study does add weight to the inference that CLL and Hodgkin's lymphoma are not capable of induction by radiation (a position adopted by the UK Compensation

Scheme). However, I suspect that it is unlikely that Hodgkin's lymphoma will be removed from the category of compensatable diseases in NIOSH-IREP, and the position of CLL must be viewed in this context.

The Trabalka and Apostoaei Report

Given the above background, the approach of Trabalka and Apostoaei is a reasonable one. CLL is a cancer that is more like a non-Hodgkin's lymphoma than an acute leukaemia or chronic myeloid leukaemia, and the lymphoma-multiple myeloma risk model currently adopted in NIOSH-IREP would seem to be the model most appropriate for application to CLL. The central point is this: if the lymphomas and multiple myeloma, especially Hodgkin's lymphoma, are considered to be compensatable on the basis of the available evidence, is it acceptable to exclude CLL from NIOSH-IREP (the only type of cancer not to be included in the NIOSH-IREP programme)? Given the evidence forming the basis for the inclusion of Hodgkin's lymphoma in the NIOSH-IREP programme, the exclusion of CLL might not be thought acceptable. Under these circumstances, the solution adopted by Trabalka and Apostoaei – basically, considering CLL to be covered by the current lymphoma-multiple myeloma risk model – is logical. The authors highlight the uncertainties, which are substantial, but then the uncertainties surrounding the application of the current lymphoma-multiple myeloma risk model in NIOSH-IREP are also substantial.

Summary

The issues can be summarised thus:

- The evidence for chronic lymphocytic leukaemia (CLL) being capable of induction by ionising radiation is weak
- The evidence for the acute leukaemias and chronic myeloid leukaemia being capable of induction by ionising radiation is strong

- CLL is more like a non-Hodgkin's lymphoma than an acute leukaemia or chronic myeloid leukaemia
- The evidence for Hodgkin's lymphoma, non-Hodgkin's lymphoma and multiple myeloma being capable of induction by ionising radiation is weak, especially the evidence for Hodgkin's lymphoma
- **However**, Hodgkin's lymphoma, non-Hodgkin's lymphoma and multiple myeloma are considered compensatable diseases under NIOSH-IREP
- The evidence for Hodgkin's lymphoma being capable of induction by ionising radiation is not materially greater than that for CLL, but Hodgkin's lymphoma is included in the current lymphoma-multiple myeloma risk model in NIOSH-IREP
- Given this, can the continued exclusion of CLL from NIOSH-IREP be justified?
- If the answer to this question is no, then it is reasonable to treat CLL in the same way as the lymphomas and multiple myeloma are currently treated in NIOSH-IREP
- Presently, the lymphomas and multiple myeloma are considered together by one risk model and this could be extended to CLL
- Consideration should be given to the implications of the anticipated publication of the results of the analysis of the updated incidence data for lymphatic and haematopoietic cancers among the Japanese atomic bomb survivors
- The results of this update could affect the approach taken by NIOSH-IREP to the lymphomas and multiple myeloma (currently considered together), and also to how CLL should be included in the programme (if at all).

Conclusion

The approach of Trabalka and Apostoaei to the treatment of CLL in NIOSH-IREP is reasonable, given the inclusion of some other cancers as compensatable in the programme for which the evidence for induction by

radiation is weak, as is that for CLL. The crux of the matter is this: if Hodgkin's lymphoma is considered as compensatable, given the evidence for induction by radiation, is it acceptable to consider CLL as non-compensatable, given the evidence for induction by radiation? If the answer to this question is no, then the approach of Trabalka and Apostoaei is logical.

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