Mediterranean Journal of Hematology and Infectious Diseases

Highlights

Who Has Therapy-Related AML?

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Potential conflict of interests: RPG is a part-time employee of Celgene Corp.

Keywords: Therapy-related leukemia; alkylators; ionizing radiations; Topoisomerase Inhibitors; DNA Repair.

Citation: Gale R.P., Bennett J.M., Hoffman F.O. Who has therapy-related AML? Mediterr J Hematol Infect Dis 2017, 9(1): e2017025, DOI: http://dx.doi.org/10.4084/MJHID.2017.025

Published: March 1, 2017 **Received: January 11, 2017** **Accepted: February 23, 2017**

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Therapy-related leukemia or *therapy-related myeloid neoplasm* are widely-used terms to designate leukemia developing in persons who previously received anti-cancer therapy (for example, see references 1 and 2), especially if the prior anti-cancer therapy included drugs such as alkylators, DNA-intercalators, topoisomerase-2-inhibitors, purines and/or ionizing radiations. Sometimes specific genes such as *RUNX1 (AML1)*, *EVI1*, *NRAS* or *KMT2A (MLL)* are mutated by therapy or gene variants inherited which activate mutagens or interfere with DNA repair, such *FANC*, *NQ01* or *AML2*.[3-5] But how can we know if AML in someone is a therapy-related?

Studies designed to explore a possible association between prior cancer-therapy and developing AML use observational databases,[6] case controls or cohort studies and diverse but imperfect statistical techniques and thus can only inform us regarding associations, not *cause-and-effect*. Data from randomized clinical trials are sometimes informative. For example, a large randomized trial[7] of different drug regimens for persons with Hodgkin disease reported a 6-fold increase in AML risk in one therapy cohort compared with the other. However, these data still to do not allow us to identify whether a specific case of AML in either cohort is therapy-related. A fundamental requirement of these studies is access to precise exposure data, including dose, schedule, age at exposure, sex, interval from exposure to outcome, potential confounders and others. It is also important to consider *biological plausibility*: are data from epidemiological studies consistent with data from experimental models and known chemical and biological mechanisms?

Consider, for example, data from the A-bomb survivors who developed AML.[7] Because exposure data are known with reasonable precision and because there is a relatively large control cohort, it is possible to estimate about one-third of the cases of AML in the exposed population were caused by or contributed to by exposure to radiation. However, which cases of AML were A-bomb-related *versus* which would have occurred anyway is virtually unknowable except for those few cases in persons exposed to very high levels of radiation dose. The probability a specific case of AML was A-bomb-related is a function of age at exposure, sex, and time between exposure and

AML diagnosis. Thus, even in this relatively controlled setting it is difficult to declare with precision whether a case of AML in an A-bomb survivor was caused or contributed to by radiation exposure.

It is sometimes possible to estimate the likelihood that an exposure caused or contributed to a person developing AML. However, this estimate includes the assumption radiation exposure may initiate new cases of AML but will not promote (accelerate) cases of AML which would also occur in the absence of exposure to anti-cancer therapy. Therefore, using estimates based entirely on epidemiological observation without explicitly accounting for underlying mechanisms of causation, results in such estimates being uncertain and potentially biased.[9,10] Thus, it is often very difficult to distinguish between cases of AML in which a therapy- exposure caused or contributed to developing AML (etiologic cases) and situations where the person would have developed AML anyway, perhaps at a later interval.

The epidemiology-based process of estimating causation described above differs radically from how haematologists determine whether AML is *therapy-related*. Often precise exposure details are unknown and/or unknowable such that the haematologist is merely guessing. However, because the diagnosis *therapy-related AML* is entered into the dataset and these data are then used to explore associations between exposures and other variables, these biases and inaccuracies become *self-fulfilling prophesies.* If you think a cytogenetic abnormality such as del(5/5q) is associated with *therapy-related AML* and enter the case as such in a dataset it is not surprising to find a correlation between del(5/5q) and *therapy-related AML* in retrospective analyses. Because del(5/5q) occurs in persons with AML who were not exposed to anti-cancer therapy and is absent in many persons with AML who received anti-cancer therapy causation experts judge this method of determining attribution to be without scientific merit. In sum, the relationship between an exposure and risk of developing *therapy-related AML* is uncertain at best. Nevertheless, these cases are often designated as *therapy-related AML* despite the uncertainties involved in making judgments and arriving at this conclusion.

The question is whether it is possible to precisely estimate whether a specific case of AML was caused by or contributed to by an exposure. As discussed above, specific exposure data are needed to make a reasonable estimate. Unfortunately, such data are usually unavailable. For most drug exposures there are no specific risk-estimators resulting in risk estimates which are qualitative, not quantitative. Quantitative risk-estimators are available for radiation exposures but are derived from exposure settings rather different than most exposures preceding AML.[11-13] Moreover, calculating probability of causation from a radiation exposure requires knowing several exposure- and subject-related variables which are typically unknown for a specific case of AML.

Another important variable is age at diagnosis. Estimates of the likelihood a case of AML is *therapy-related* need to consider a markedly higher background AML incidence in older persons after identical exposures. Other important adjustments are for tobacco exposure and exercise, both of which are reported to be associated with AML, as are exposures to chemicals such as benzene, chloramphenicol *etc*. Given these considerations it is unlikely or impossible an evaluating physician can *accurately* estimate whether a case of AML in a person who received prior cancer-therapy is *therapy-related*.

Communicating the likelihood that a case of AML is *therapy-related* requires expressing some measure of the reliability of the estimate. The uncertainty range could be derived from epidemiological studies, clinical trials or from experts with diverse opinions about relationships between past exposure(s) and a specific case of AML along with knowledge about the mechanisms of exposure-induced causation. Usually the *best estimate value* is of greatest interest to the haematologist. However, the width of a credibility limit about the *best estimate value* provides important additional information about estimate reliability. For example, a *best estimate value* of 20 percent with a 95 percent credibility limit of 0 to 70 percent indicates, on average, that it is unlikely that the specific case of AML is *therapy-related* but the underlying supporting evidence is highly uncertain. In contrast, a *best*

estimate value of 75 percent with a 95 percent credibility of 55 to 85 percent indicates a reasonably high chance that a specific case of AML is *therapy-related*. However, even here, there remains a reasonable chance the case is not *therapy-related*.

There are many consequences of a *reasonably accurate* estimate of whether a person's AML is *therapy-related*. For example, deciding whether to give intensive, non-intensive, or no therapy may be influenced by this estimate. Another example is whether to consider a hematopoietic cell transplant. For each of these therapies, and others, an imprecise or incorrect estimate of whether AML is *therapy-related* can result in under- or over-treatment. Thus, being able to accurately estimate whether AML is *therapy-related*, as well as communicating the reliability of any estimate given, is important.

In summary, we suggest caution designating a specific case of AML as *therapy-related* without convincing data this is so. When data are insufficient to make a reasonable *best estimate value* about therapy-induced causation of a case of AML, one should also convey the level of certainty/uncertainty using qualitative terms such as *likely*, *unlikely* or *uncertain*.

Acknowledgement. RPG acknowledges support from the NIHR Biomedical Research Centre funding scheme.

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