In this issue of the Journal, Mukherjee and colleagues at the Cleveland Clinic report that prostate cancer patients receiving radiation therapy (RT) at their center are no more likely to develop a therapy-related myelodysplastic syndrome than patients undergoing radiation-free radical prostatectomy (1). To properly frame the importance of this finding, it is important to understand several discoveries leading up to this report.

In 2008, the World Health Organization created the descriptive entity “therapy-related myeloid neoplasms” (t-MNs), which encompasses such conditions as therapy-related myelodysplastic syndrome (MDS) and therapy-related acute myeloid leukemia (AML) based on the following observations: 1) approximately 30% of all MDS cases and 10% to 30% of all AML cases arise after chemotherapy and/or RT for an antecedent cancer; 2) t-MNs harbor distinct chromosome and genetic abnormalities; and 3) patients with t-MNs had worse clinical outcomes compared with patients with de novo MDS or AML (2).

But not all therapies trigger a t-MN clone. Systemically administered alkylating agents and topoisomerase II inhibitors are known carcinogens of hematopoiesis. After these chemotherapies, secondary MDS and AML clones often harbor unfavorable cytogenetic abnormalities. Alkylating agents induce loss of all or part of chromosomes 5 or 7, in addition to deletions or mutations in the P53 tumor suppressor gene. Topoisomerase II inhibitors cause gene rearrangements involving MLL and RUNXI/AML1 genes. These unfavorable genetic abnormalities portend a short survival time.

However, t-MN incidence after ionizing radiation is more complex. High-dose total body irradiation, such as in a nuclear bomb blast or conditioning therapy before hematopoietic cell transplant, is a known leukemogenic. Combined modality therapy, including both RT and radio-sensitizing chemotherapy, is also associated with more aggressive and treatment resistant t-MNs with unfavorable cytogenetic abnormalities (3).

But the leukemogenic potential of lower doses of RT, such as that used in prostate cancer, breast cancer, and lymphoma, is up for debate. Certainly advancements in imaging, radiation planning, and radiation techniques have permitted a tighter focus on the target tumor bed and decreased radiation exposure outside of the bed, thus sparing normal tissues such as the bone marrow from DNA-damaging photons. Moreover, when analyzing MDS and AML clones arising years after RT alone, these myeloid neoplasia clones are actually more similar to de novo MDS and AML in terms of cytogenetic characteristics and clinical behavior (3). Together, these compelling observations suggest that modern RT alone may not be as leukemogenic as combined modality treatment or total body irradiation—an important hypothesis worthy of testing when considering the increased number of cancer survivors after RT.

Before rushing to the conclusion that RT alone is free of leukemogenic potential, it is important to address the question from the direction of a solid-tumor patient. Up until this point, oncologists studied t-MN incidence by first finding t-MN patients and then parsing their characteristics based on prior therapy (RT vs chemotherapy vs combined modality vs surgery). In these retrospective analyses, the potential for selection bias is large. In contrast, the real questions are 1) whether solid tumor patients treated with RT alone go on to develop t-MNs at a rate higher than radiation-free counterparts and 2) how post-RT t-MN pathobiology and clinical outcomes compare with those of radiation-free cohorts. Both of these questions require a forward perspective starting from the solid-tumor patient.

The report by Mukherjee et al. in this issue of the Journal is one of the first attempts to answer the question of the relation of t-MNs to RT from the standpoint of the solid-tumor patient (1). Specifically, the investigators combined databases from one large cancer center so they could follow the fate of all prostate cancer patients and development of a subsequent MDS. In their report, they found no difference in incidence of MDS between prostate cancer patients treated with RT versus prostate cancer patients treated with radical prostatectomy.

Before making conclusions, a few considerations should be made when interpreting the data. First, small sample size is a limitation of the study. With only 31 MDS cases identified, a limited number of conclusions can be made. However, 31 case patients with MDS out of 10924 older prostate cancer survivors is on par with incidence estimates from large, population-based cancer registries and billing code studies (4,5). Furthermore, this low event rate of MDS speaks to the investigators’ main point that modern RT alone does not increase MDS incidence beyond that of its radiation-free counterparts or beyond incidence levels in the general population. A second consideration is the short follow-up time in this study. Whereas the latency period between finishing prior therapy and diagnosis of a t-MN is typically 1 to 7 years depending on the prior therapy, the median follow-up time in this study was 3 years. Early follow-up may miss MDS cases. However, the median follow-up time in the group predicted to have the greatest risk of developing secondary MDS, the external beam radiation therapy (EBRT) cohort, was 6.8 years. This length of follow-up may have been long enough for MDS to declare itself. The shortest follow-up time was in the surgery cohort.
(1.9 months). However, waiting longer to find more case patients with MDS in this radiation-free group would only further support the investigators’ thrust that MDS occurs at comparable rates in prostate cancer patients regardless of therapy choice. A third consideration is the cytogenetic characteristics. Although the data show no difference in cytogenetic risk category among the groups (EBRT vs brachytherapy vs surgery), the EBRT group is missing cytogenetic data in 50% of patients, the brachytherapy group is missing data in 11%, and the surgery group is missing data in 0%. It is possible that the missing cytogenetic data in the RT groups (EBRT and brachytherapy) may fit into different risk categories, and with so few incident case patients (n = 31) the new data could have large effects. That being said, the missing data appear to be primarily in patients with lower-risk MDS and MDS in evolution, which often do not have high-risk cytogenetics.

The small cohort presented by Mukherjee and colleagues in this issue of the Journal adds to mounting evidence that modern RT alone may not trigger t-MNs. However, larger studies with longer follow-up time are needed to confirm their important findings. Additionally, t-MNs after emerging radiation modalities such as proton beam therapy merit investigation. Finally, the t-MN genotype deserves much deeper interrogation than chromosome karyotyping. With a new appreciation of MDS as a multigenetic and subclonal disease (6–8), it is possible that recurrent genetic mutations, undetected by conventional Giemsa banding technique, are found in t-MNs after RT alone and distinguish RT-related t-MNs from chemotherapy-related t-MNs and de novo myeloid neoplasias. A distinct molecular genetic signature in RT-related myeloid neoplasias, if present, could lead to important discoveries of genetic predisposition and therapeutic choice specific to those individual solid-tumor patients receiving RT and developing a subsequent myeloid neoplasm.

References


Notes

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