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Myeloid malignancies after treatment for solid tumours

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ABSTRACT

The cure rate for several solid tumour malignancies including breast cancers, head and neck cancers, bone cancers, and sarcoma has improved remarkably with the advent of neoadjuvant and adjuvant therapies. Unfortunately, exposure to chemotherapy or radiation as a part of these treatments exposes patients to the risk of subsequent myeloid malignancies. Therapy related myeloid malignancies have certain characteristic findings. They typically arise within 10 years of treatment exposure, they are seen in younger patients, and the greatest risk is in patients who receive therapy with alkylating agents or topoisomerase II inhibitors. Solid tumours whose therapies utilize these agents at higher doses, namely bone/soft tissue cancers, testicular cancer, anal cancer, and brain tumours, appear to be the groups at highest risk for T-MN. Beyond these patients, emerging populations diagnosed with T-MN include prior platinum exposure, and patients requiring G-CSF support with chemotherapy.

1. Introduction

Solid tumours including those arising from organs such as lung, breast, colorectal, and prostate contribute to the vast majority of cancer diagnoses worldwide. With advances in early diagnosis and definitive therapy, a significant proportion of these patients are considered cured. As of Jan 2016, the US has nearly 15.5 million cancer survivors. The number of survivors is projected to increase to 20.3 million by the year 2026 [1]. Unfortunately, some of these patients with a previously treated solid tumour subsequently develop a haematological neoplasm of myeloid lineage. Most commonly, the practice of using chemotherapy or radiotherapy (RT) to treat patients with solid tumours is thought to increase the risk of developing a spectrum of myeloid neoplasms known as therapy related myeloid neoplasms. This group of hematologic malignancy is widely recognized as an emerging challenge in the current era, given that newer therapies are improving the life expectancy of patients with solid tumours. The World Health Organization (WHO) 2001 classification initially described this entity as either therapy related acute myeloid leukaemia (t-AML) and therapy related myelodysplastic syndrome (t-MDS) [2]. Both these subtypes have common clinical features and very poor prognosis which led to the revision of nomenclature in the 2008 WHO classification that merged these two subtypes under one entity “therapy related myeloid neoplasm”(T-MN) [3]. Apart from T-MN, other malignancies such as chronic myeloid leukaemia (CML) and myeloproliferative neoplasm (MPN) have also been described after treatment of a prior solid tumour malignancy, although the causal relationship between solid tumours and these myeloid neoplasms is not well established [4,5].

Prognosis of T-MN has generally remained dismal with an overall survival (OS) ranging from 8 to 10 months [6]. Factors such as biological resistance to treatment, adverse cytogenetic features, comorbid conditions, and poor bone marrow reserve from prior chemotherapy leading to inability in tolerating intensive treatments have adversely affected the prognosis of this disorder. In the

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recent era, strategies such as newer chemotherapies and allogeneic hematopoietic cell transplantation, along with better supportive care and offer hope for an improvement in the outcomes of these patients in the future. In this review, we will primarily focus on the factors contributing to the development of myeloid neoplasms after therapy for prior solid tumours.

2. Epidemiology

Therapy-related myeloid neoplasms represent only a small portion of newly diagnosed AML, estimated at < 10% of the newly diagnosed cases. Our most recent study of T-MN using the SEER database from US demonstrated an incidence of 0.13/100,000 individuals, and this is consistent with the incidence described from other parts of the world [8,9]. The median age at diagnosis is 65 years, and most of these patients are females, thought due to the high incidence and prevalence of breast cancer requiring therapy [8]. Minority races have been found to have a lower disease incidence than whites, hypothesized due to the disparities in access to care and a shorter survival in the context of primary malignancy [8,10].

The median latency period to develop T-MN is typically between 1 and 10 years, with the highest risk in the first 5 years. Younger age at exposure to chemotherapy has been linked to an increased risk of subsequent development of T-MN [7]. Although therapy for any solid malignancy can predispose to this disorder, the risk appears to be pronounced for bone/soft tissue, testes, and ovary [7]. Among patients treated with chemotherapy and/or radiation for any tumour, the estimated risk of developing subsequent therapy related AML is 4.70 times greater compared to general population [7]. Due to evolving treatment strategies in a number of solid tumours, the risks for T-MN after a preceding solid tumour is changing. Morton et al. found that patients with oesophageal, cervical, prostate, and anal cancers treated with chemotherapy had elevated risk of t-AML after the year 2000, and a similar trend was also seen after treatment for bone/joint and endometrial cancers since 1990s [7]. However, the risk was found to be decreasing over time since 1975 for patients with ovarian cancer, possibly due to the changes in the use of cytotoxic regimens for these diseases over time [7].

3. Risks from chemotherapy

Alkylating agents and topoisomerase inhibitors are two most common groups of drugs that have been long linked to the development of therapy-related myeloid neoplasms with differing characteristics [11]. However, there are reports of T-MN arising from other agents as well as described below. Over the years, an increase in the proportion of solid tumour patients treated with chemotherapy has been observed, particularly for cancers of head/neck, oesophagus, gastric, colorectal, anal, lung, female breast, cervix, and brain [7] which potentially contributes to the temporal rise in T-MN cases.

3.1. Alkylating agents

Alkylators are one of the oldest anticancer agents used for the treatment of solid tumours, derived from the first alkylator – nitrogen mustard. Initially, this was used as a chemical weapon particularly during the World Wars, and subsequently noted to have bone marrow suppressive properties. The seminal work by Gilman and Goodman demonstrated the activity of these agents in lymphomas that led to the FDA approval of mechlorethamine in 1949 [12]. Common alkylators used for the treatment of solid tumours include cyclophosphamide, ifosfamide, and temozolomide. Previously utilized agents include melphalan, which were once used for the treatment of solid tumours like breast cancer are not commonly used anymore. Overall, about 21% of patients received an alkylating agent as part of initial cancer therapy [43].

The leukemogenic potential of alkylators has been known for many years, characterized by a longer latency period that is often preceded by myelodysplasia related changes. Many prior series have demonstrated that chromosomal deletions involving the 5q and 7q regions are common in these patients [13,14]. These chromosomal losses often lead to defects in several genes that are involved in haematopoiesis and trigger the progression to leukaemia [15,16]. While alkylators generally work by adding an alkyl group to the guanine base of the DNA leading to impaired replication and transcription, the leukemogenicity is potentially a two-step process with chromosomal loss and the resultant tumour suppressor allele loss being the first hit, followed by second hit that transforms into leukaemia [17]. This also explains the long latency period and antecedent myelodysplasia related changes in these patients.

3.2. Topoisomerase inhibitors

DNA topoisomerases are enzymes that are critical for cellular function by regulating DNA winding through removal of knots and tangles [18]. They execute important cellular activities such as ensuring DNA stability during replication. Inhibitors of topoisomerases cause cell damage by trapping the enzymes in covalent complexes on the DNA and can be classified into two types- Topoisomerase I inhibitors such as irinotecan, topotecan and topoisomerase II inhibitors such as etoposide, doxorubicin, daunorubicin and mitoxantrone. They are used in the treatment of many solid tumours such as lung cancer, colorectal cancer, pancreatic cancer, prostate cancer and sarcomas. The most recent studies estimate that only 12% of patient received a topoisomerase II inhibitor as part of initial cancer treatment [43].

Topoisomerase inhibitor associated T-MN is characterized by a shorter latency period of 1–2 years from exposure, typically without any antecedent myelodysplastic syndrome (MDS). The occurrence of t-MN also appears to depend on the specific regimen, total dosage, and the schedule employed. Importantly, an association between t-MN from these agents and abnormalities in the MLL gene at chromosome 11q23 had been identified with a different natural history and clinical features as originally described by

Pedersen-Bjergaard and colleagues [19]. The MLL gene affected by these agents usually encodes a multidomain transcriptional regulatory protein involved in epigenetic regulation of several pathways. It is unclear how topoisomerase inhibitors induce T-MN, but appears that the characteristic chromosomal abnormalities are initiated through DNA breaks from these agents rather than selection of pre-existing clones which harbour these translocations in the marrow [18].

3.3. Other cytotoxic agents

The risk of therapy related myeloid neoplasm with other commonly used cytotoxic agents is less known given the lack of systematic studies exclusively focusing on these agents. More often, it becomes difficult to separate the risk associated with these agents as they are often given along with alkylators or topoisomerase inhibitors as a part of combination chemotherapy. Nevertheless, there are reports of therapy related leukaemia and MDS associated with platinum agents, 5-FU, capecitabine, and taxanes [20–23]. Platinum agents, which include carboplatin and cisplatin, have seen increased use among lung cancer, gastrointestinal cancers, head and neck cancers, and ovarian cancer, and overall 60% of all patients receiving initial chemotherapy receive a platinum agent. Therefore, as these agents are increasingly being incorporated into solid tumour regimens, there is a need for more research to further define the association, and also the mechanism by which these agents drive development of T-MN.

3.4. Newer agents

In addition to conventional chemotherapeutic agents, newer agents such as poly ADP polymerase (PARP) inhibitors have been associated with a risk of t-MN [24,25]. PARP includes a family of multifunctional enzymes that influences cell differentiation and repair of DNA breaks. Inhibition of PARP leads to accumulation of DNA breaks at replication forks and resultant tumour cytotoxicity in patients who lack DNA repair complexes such as BRCA1 and BRCA. The current FDA approved PARP inhibitors include olaparib, rucaparib, and niraparib for the treatment of patients with advanced ovarian cancer. In addition, many other solid tumours are currently investigating the role of PARP inhibitors either in clinical trials or as off-label use based on the molecular profile. Although the mechanism behind therapy myeloid neoplasm arising from PARP inhibitors is unclear, additional defects in DNA repair pathways could increase this risk and needs to be explored in the future.

4. Risks from radiation therapy

While the role of chemotherapy in the pathogenesis of t-MN has been well studied, radiation induced t-MN had been difficult to study as most of the radiation therapy (RT) approaches also concurrently use chemotherapy. A recent population-based cohort study from the US by Teepen et al. has provided some information on the individual risk of t-MN after RT [26]. In this study, they included patients with thyroid, prostate, and uterine cancers treated exclusively with RT from 2000 to 2013. This showed a significantly elevated risk of myeloid malignancies in these patients. The risk of AML after RT was elevated in patients with thyroid cancer (SIR = 2.77), prostate cancer (SIR = 1.14), and uterine cancer (SIR 1.77), including the individual subtypes of AML such as those with cytogenetic abnormalities, APL, and AML with myelodysplasia-related changes. They also found an increased risk of CML after RT for thyroid cancer (SIR = 5.38) and prostate cancer (SIR = 2.11). No significant risk for MPNs and MDS/MPNs were reported. Factors such as the type and dose of RT play an important role in the risk of developing subsequent myeloid neoplasms. While the latency period for development of t-MN is longer after chemotherapy, the risk appears to be shorter after exposure to agents such as radioactive iodine for treatment of thyroid cancer (median 2.9 years) [27]. It has also been postulated that radiation exposure is effective in inducing balanced chromosomal translocation that can lead to development of CML [28].

5. Risks from growth factor use

Increasing use of intensified chemotherapy regimens, as well as increasing treatment of frailer, or older patients with solid tumours has led to increased incorporation of growth factors such as G-CSF during cancer therapy. G-CSF, through stimulation of haematopoiesis during a period of chemotherapy exposure, has been hypothesized as a risk factor for subsequent T-MN development. In a study evaluating risk factors among breast cancer patients who subsequently developed T-MN, G-CSF use, independent of chemotherapy or radiotherapy, was associated with an increased risk (RR = 4.16; 95% CI, 1.2–14.3, P = 0.02) for T-MN development [29]. This increased risk was additionally discovered among patients enrolled in an NSABP adjuvant chemotherapy study who subsequently developed T-MN [30]. Finally, a systematic review including non-breast cancer patients, compared T-MN rates among patients receiving chemotherapy with growth factor compared to without [31]. This demonstrated a higher relative risk (1.92, 95% CI 1.19–3.07, P = 0.007) of T-MN among patients who received growth factor [31].

6. Pathogenesis

T-MN results from a complex interplay of several factors such as age, genetics, environment, and therapeutic modalities such as chemotherapy or radiation. Over the last few years, several studies have tried to address the pathogenesis of this disorder. While the exact mechanism by which it arises is still unknown, several possible underlying mechanisms have been proposed. Exposure to chemotherapeutic agents such as alkylators or topoisomerase inhibitors was initially thought to induce direct DNA damage resulting in adverse chromosomal alterations and genetic mutations that evolve into T-MN [32].

Exposure to agents that induce DNA damage likely contribute partly; more recently, the role of selective expansion of pre-existing clones has also been proposed in the disease pathogenesis. An experimental study by Wong et al. demonstrated that patients with t-MN had detectable mutations at a lower frequency in genes such as TP53 and ABC transporters even 3–6 years prior to the onset of t-MN and before use of any prior chemotherapy [33]. After subsequent exposure to therapy, these TP53 clones expanded selectively suggesting their ability to survive despite exposure to chemotherapy and gaining significant growth advantage leading to the development of T-MN. Another mechanism which is implicated in the disease pathogenesis is the presence of clonal genetic abnormalities without evidence of any underlying haematological disorder, also known as clonal haematopoiesis of indeterminate potential (CHIP) [34]. Mutations in genes such as DNMT3A, TET2, ASXL1 and TP53 contribute to the spectrum of CHIP lesions that is linked to the development of cancer [34]. It has been demonstrated that these CHIP lesions such as TP53 have selective advantage of expansion and becoming pathological in the setting of exposure to chemotherapy. Similarly, patients with lung, breast and ovarian cancer have been noted to have CHIP mutations in PPM1D gene, a serine/threonine phosphatase that negatively regulates p53 function [35,36]. A truncating mutation in this gene causes gain of function, leading to suppression of p53 activity and clonal outgrowth after treatment [37]. This hypothesis, in part, could explain why increasing cases of T-MN are being diagnosed after exposure to chemotherapeutic agents such as platinum compounds, as opposed to agents traditionally implicated in T-MN.

Inherent risk factors that predispose to subsequent myeloid neoplasm should also be considered as AML/MDS could occur after decades of exposure to chemotherapy or radiation raising the question of whether they are truly therapy related. While some of this might be pure stochastic effect leading to a second cancer, some patients have underlying inherited mutations in genetic pathways that predispose them to multiple malignancies. A study by the German AML Group showed that about 3% of patients developing AML had a prior malignancy that was never treated with chemotherapy or radiation and these patients more often had prostate, bladder, and renal cell carcinoma [38]. T-MN has been associated with certain germ line variants in genes of the DNA damage response pathway such as BRCA, BARD1, and TP53 [39]. Cumulatively, these biological factors in addition to polymorphisms in drug metabolizing enzymes and changes in the bone marrow stromal microenvironment could lead to the development of myeloid malignancies after solid tumours (see Fig. 1).

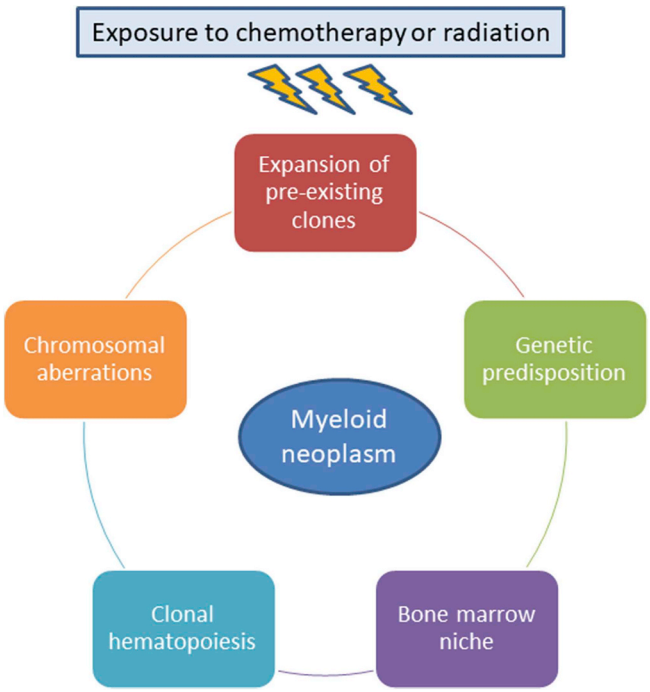

Fig. 1. Illustrates T-MN pathogenesis outlined above.

7. Specific tumour types

7.1. Breast cancer

Breast cancer represents the commonest cancer diagnosis in the United States with an estimated 268,670 new cases in 2018 [40]. Due to its high incidence, breast cancer patients account for the largest population of patients receiving chemotherapy and radiotherapy. As such, breast cancer contributes to the majority of T-MN cases in most studies [7]. Population-based studies from US have demonstrated that the risk of T-MN in patients with breast cancer is higher than the general population, (SIR 4.60), but a lower

relative risk compared to patients treated for other cancers including soft tissue/bone cancers, or testes cancer.

Treatment for breast cancer has evolved since the 1970s. Previously, melphalan and regimens such CMF (cyclophosphamide, methotrexate, and fluorouracil) used to be common agents for breast cancer therapy. These agents led to a higher incidence of T-MN [41,42]. The current standard of care includes regimens that are either anthracycline based (doxorubicin, cyclophosphamide, taxanes) or non-anthracycline based (docetaxel, cyclophosphamide) with or without radiotherapy. Within anthracycline based therapy, patients may receive standard doses of cyclophosphamide (600mg/m2) or intensified doses (2400mg/m2). Dose intensification was facilitated by G-CSF use. Overall, while dose intensification has resulted in better breast cancer control, an NSABP study revealed that intensification led to a higher incidence of T-MN [30]. Overall, the cumulative incidence of T-MN at 5 years after treatment with intensified doses of cyclophosphamide was 1.01% vs 0.21% in patients treated with standard cyclophosphamide dosing [30].

At present, anthracycline based adjuvant chemotherapy remains the standard for the treatment of breast cancer, however the practice of using risk adapted chemotherapy in the adjuvant setting could potentially decrease the T-MN risk in future [21].

7.2. Soft tissue/bone cancer

Bone cancers including Ewing sarcoma are overall infrequent, most commonly occurring in adolescents. Treatment commonly includes a multimodal approach of surgery, radiation and adjuvant chemotherapy. Due to the infrequency of this malignancy, the number of cases of T-MN overall after diagnosis is small. Despite that, the risk of developing T-MN is higher in this group compared to other solid tumour survivors, with an SIR of 39 (95% CI 21.4–65.5) for bone cancers and 10.4 (95% CI 6.4–15.9) among soft tissue cancer patients [43].

The significant increased risk in this population has been attributed to the chemotherapy regimens used in this population. Often, multi-agent chemotherapy regimens which include doxorubicin or ifosfamide are utilized in this group. Standard therapy for Ewing sarcoma, for instance, includes doxorubicin, vincristine, cyclophosphamide, and dactinomycin as well as ifosfamide and etoposide. The effect of this regimen, evaluated by reviewing outcomes in patients enrolled in INT-0091, revealed a cumulative incidence of T-MN at 5 years estimated at 2%, which is significantly higher than the general population [44]. While these regimens pose a high risk for T-MN, the response rate, particularly for Ewing sarcoma, remains high, and therefore careful monitoring must be prescribed for this patient group given the risk of subsequent T-MN [44].

7.3. Ovarian/gynecological cancer

Among gynaecologic malignancies, cervical, ovarian, and uterine cancers are commonly treated with chemotherapy and/or radiation that puts them at risk for T-MN. Population based studies from US have demonstrated a higher risk of T-MN in patients with cervical (7.29), ovarian (SIR 8.68), and endometrial cancer (SIR 5.97) as compared to the general population [7].

Platinum based chemotherapy, mainly cisplatin, in combination with radiation therapy, represents the standard for cervical cancers. In ovarian cancer, alkylating agents such as melphalan were a major component of therapy, and this contributed to a higher risk of T-MN [45]. Current treatment strategies utilize platinum-based chemotherapy, commonly carboplatin, and taxanes, commonly paclitaxel. Overall, while there has been a slight decrease in the incidence of T-MN, the risk is still higher as compared to the general population [7,46]. In the future, with incorporation of PARP inhibitors into clinical practice, particularly in combination with platinum based chemotherapy, careful follow-up is required in this group to determine what the effect will be in the development of T-MN.

7.4. Other solid tumours

Certain less common solid tumour malignancies are associated with a higher risk of subsequent T-MN development. Testicular cancer is an example where there is a higher risk for T-MN, as standard treatment incorporates alkylating agent therapy. These patients are estimated to have higher risk of T-MN with an SIR of 12.3 (95% CI 7.6–18.8) [43]. Incorporation of bleomycin, and/or ifosfamide, in combination with platinum chemotherapy, is thought to contribute to the higher risk of T-MN among testicular cancer patients receiving chemotherapy. Further, survivors of brain/CNS cancer are at higher risk for T-MN with an SIR 7.2 (95% CI 4.6–10.8) [43]. This is thought to be attributed to temozolamide use in this population. Finally, while colorectal cancer patients generally are not thought to have an increased risk for T-MN, Anal cancer has been associated with an increasing risk for T-MN with an SIR of 3.6 (95% CI 2.4–5.1) [43]. Mitomycin, an alkylating agent, which has been incorporated into standard care for anal cancers during the 1990s along with 5-FU and possibly XRT, has resulted in an increasing incidence of T-MN among anal cancer patients over the past few decades.

8. Conclusion

Therapy-related myeloid neoplasms represent an uncommon but growing population of patients presenting with a myeloid neoplasm. A combination of chemotherapy and/or radiation exposure and underlying aberrant clones within the bone marrow create the groundwork for the development of a t-MN. Among solid tumour patients, breast cancer patients represent the greatest number of patients who go onto developing T-MN, however their risk of development is only slightly increased, and stable. Evolving treatment strategies have otherwise resulted in a high risk for T-MN among patients with rare tumours such as Ewing sarcoma, testicular cancer, brain cancer.

In the future, a deeper understanding of T-MN after platinum chemotherapy is necessary. The majority of solid tumour patients receiving platinum based chemotherapy is rising, as is the number of patients who subsequently develop T-MN after this exposure. Further, the development of methods to identify patients at risk for t-MN will be an important step toward further improving outcomes for these patients. Our increasing ability to identify abnormal molecular findings among the blood and marrow of patients through next generation sequencing techniques should allow some ability to predict which patients are more susceptible upon exposure to chemotherapy and/or radiation. While modification of treatment plans for solid tumours may not be feasible, at a minimum, enhanced surveillance could allow for the detection of early myeloid changes. Finally, clinical trials evaluating protective or preventative interventions may be developed.

Conflicts of interest

The authors of this manuscript have no conflicts to disclose at the time of submission.

Practice Points:

- Alkylating agent chemotherapy, topoisomerase II inhibitor chemotherapy, and radiation therapy for the treatment of solid tumours are all risk factors for the development of therapy related myeloid neoplasms (T-MN)
- Growth factor use and platinum-based chemotherapy likely increases the risk for T-MN
- The greatest number of patients seen with therapy related myeloid neoplasms are patients treated for breast cancer.
- The greatest risk for therapy related myeloid neoplasms are seen in patients treated bone/soft tissue malignancies, testicular cancer, and ovarian cancer.

Research Agenda:

- Underlying clonal haematopoiesis may represent the underlying link leading to therapy related myeloid neoplasm, and should be assessed in the clinical trial setting among patients receiving potentially curative interventions for solid malignancies
- Further research investigating mechanisms for T-MN after non-traditional exposures (i.e. after Platinum chemotherapy, PARP inhibitors) will help to better understand the patients we will see with T-MN in the future.

References

[1] American Cancer Society. Cancer treatment & survivorship facts & figures 2016-2017. Atlanta: American Cancer Society; 2016.
[2] Brunning RD, Matutes E, Borowitz M. Acute leukaemias of ambiguous lineage. Lyon, France: WHO classification of tumours of the haematopoietic and lymphoid tissues IARC press; 2001.
[3] Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloidneoplasms and acute leukaemia: rationale and important changes. Blood 2009;114:937–51.
[4]. Therapy related-chronic myelomonocytic leukaemia (CMML): Molecular, cytogenetic, and clinical distinctions from de novo CMML.
[5] Incidences and outcomes of therapy-related chronic myeloid leukaemia in the era of tyrosine kinase inhibitors: surveillance of the CML Cooperative Study Group. Leuk Res 2017 Mar;54:55–8.
[6] Kern W, Haferlach T, Schnittger S, Hiddemann W, Schoch C. Prognosis in therapy-related acute myeloid leukaemia and impact of karyotype. J Clin Oncol 2004;22(12):2510–1.
[7] Morton LM, Dores GM, Tucker MA, Kim CJ, Onel K, Gilbert ES, et al. Evolving risk of therapy-related acute myeloid leukaemia following cancer chemotherapy among adults in the United States, 1975-2008. Blood 2013;121(15):2996–3004.
[8] Guru Murthy GS, Hamadani M, Dhakal B, Hari P, Atallah E. Incidence and survival of therapy related myeloid neoplasm in United States. Leuk Res 2018;71:95–9.
[9] Ong DM, Farrugia H, Wei A. Therapy-related acute myeloid leukaemia and myelodysplastic syndrome in Victoria, Australia 2003-2014. Intern Med J 2018;48(7):822–9.
[10] O'Keefe EB, Meltzer JP, Bethea TN. Health disparities and cancer: racial disparities in cancer mortality in the United States, 2000-2010. Front Public Health 2015 Apr 15;3:51.
[11] McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. Nat Rev Cancer 2017;17(9):513–27.
[12] Goodman LS, Wintrobe MM, Dameshek W, Goodman MJ, Gilman A, McLennan MT. Nitrogen mustard therapy: use of methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. JAMA 1984;251(17):2255–61.
[13] Le Beau MM, Albain KS, Larson RA, et al. Clinical and cytogenetic correlations in 63 patients with therapy-related myelodysplastic syndromes and acute nonlymphocytic leukemia: further evidence for characteristic abnormalities of chromosomes no. 5 and 7. J Clin Oncol 1986;4:325–45.
[14] Smith SM, Le Beau MM, Huo D, et al. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood 2003;102(1):43–52.
[15] LeBeau MM, Espinosa III R, Neuman WL, et al. Cytogenetic and molecular delineation of the smallest commonly deleted region of chromosome 5 in malignant myeloid diseases. Proc Natl Acad Sci USA 1993;90:5484–8.
[16] Liang H, Fairman J, Claxton DF, et al. Molecular anatomy of chromosome 7q deletions in myeloid neoplasms: evidence for multiple critical loci. Proc Natl Acad Sci USA 1998;95:3781–5.
[17] Davies SM. Therapy-related leukemia associated with alkylating agents. Med Pediatr Oncol 2001;36(5):536–40.
[18] Pendleton M, Lindsey Jr. RH, Felix CA, Grimwade D, Osheroff N. Topoisomerase II and leukemia. Ann N Y Acad Sci 2014;1310:98–110.
[19] Andersen MK, Johansson B, Larsen SO, Pedersen-Bjergaard J. Chromosomal abnormalities in secondary MDS and AML: relationship to drugs and radiation with specific emphasis on the balanced rearrangements. Haematologica 1998;83:483–8.
[20] Park HJ, Choi JH, Lee KA, et al. A case of therapy-related acute myeloid leukemia following 5-fluorouracil chemotherapy. Korean J Intern Med 2012 Mar;27(1):115–7.

[21] Carneiro BA, Kaminer L, Eldibany M, et al. Oxaliplatin-related acute myelogenous leukemia. Oncol 2006;11(3):261–2.
[22] Shapiro S, Hughes G, Al-Obaidi MJ, et al. Acute myeloid leukaemia secondary to treatment with capecitabine for metastatic colorectal cancer. Eur J Haematol 2007 Jun;78(6):543–4.
[23] Bhatnagar UB, Singh D, Glazyrin A, Moormeier J. Paclitaxel induced MDS and AML: a case report and literature review. Case Rep Oncol Med 2016;2016:8308179.
[24] Sella T, Stone RM. The impact of new drugs for breast and ovarian cancer on the occurrence of therapy-related myeloid neoplasms: understanding the baseline incidence. Gynecol Oncol 2018;151(2):187–9.
[25] Zhu J, Tucker M, Wang E, et al. Acute myeloid leukemia after olaparib treatment in metastatic castration-resistant prostate cancer. Clin Genitourin Cancer 2017;15(6):e1137–41.
[26] Teepen JC, Curtis RE, Dores GM, et al. Risk of subsequent myeloid neoplasms after radiotherapy treatment for a solid cancer among adults in the United States, 2000-2014. 2018 May 24. https://doi.org/10.1038/s41375-018-0149-2. Leukemia.
[27] Oluwasanjo A, Pathak R, Ukaigwe A, Alese O. Therapy-related acute myeloid leukaemia following radioactive iodine treatment for thyroid cancer. Cancer Causes Control 2016;27(1):143–6.
[28] Gale RP, Hlatky L, Sachs RK, Radivoyevitch T. Why is there so much therapy-related AML and MDS and so little therapy-related CML? Leuk Res 2014;38(10):1162–4.
[29] Le Deley MC, Suzan F, Cutuli B, Delaloge S, Shamsaldin A, et al. Antracyclines, mitoxantrone, radiotherapy, and granulocyte colony-stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast cancer. J Clin Oncol 2007;25(3):292–9.
[30] Smith RE, Bryant J, DeCillis Anderson S. Acute myeloid leukemia and myelodysplastic syndrome agter doxorubicin-cyclophosphamide adjuvante therapy for operable breast cancer: the national surgical adjuvant breast and bowel project experience. J Clin Oncol 2003;21(7):1195–204.
[31] Lyman GH, Dale DC, Wolff DA, Culakova E, Poniewierski MS, et al. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: a systematic review. J Clin Oncol 2010;28(17):2914–24.
[32] Heuser M. Therapy-related myeloid neoplasms: does knowing the origin help to guide treatment? Hematol Am Soc Hematol Educ Progr 2016;2016(1):24–32.
[33] Wong TN, Ramsingh G, Young AL, Miller CA, Touma W, Welch JS, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature 2015;518(7540):552–5.
[34] Genovese G, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 2014;371(26):2477–87.
[35] Ruark E, Snape K, Humburg P, et al. Breast and ovarian cancer susceptibility collaboration; wellcome trust case control Consortium.Mosaic PPM1D mutations are associated with predisposition to breastand ovarian cancer. Nature 2013;493(7432):406–10.
[36] Zajkowicz A, Butkiewicz D, Drosik A, Giglok M, Suwi´nski R, Rusin M. Truncating mutations of PPM1D are found in blood DNA samples of lung cancer patients. Br J Cancer 2015;112(6):1114–20.
[37] Kleiblova P, Shaltiel IA, Benada J, et al. Gain-of-function mutations of PPM1D/Wip1 impair the p53-dependent G1 checkpoint. J Cell Biol 2013;201(4):511–21.
[38] Kayser S, Dohner K, Krauter J, et al. German-Austrian AMLSG. The impact of therapy-related acute myeloid leukaemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 2011;117(7):2137–45.
[39] Schulz E, Valentin A, Ulz P, et al. Germline mutations in the DNAdamage response genes BRCA1, BRCA2, BARD1 and TP53 in patients with therapy related myeloid neoplasms. J Med Genet 2012;49(7):422–8.
[40] American Cancer Society. Cancer facts and figures 2018. Atlanta, Ga: American Cancer Society; 2018.
[41] Curtis RE, Boice Jr. JD, Stovall M, et al. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. N Engl J Med 1992;326(26):1745–51.
[42] Valentini CG, Fianchi L, Voso MT, et al. Incidence of acute myeloid leukemia after breast cancer. Mediterr J Hematol Infect Dis 2011;3(1). e2011069.
[43] Morton LM, Dores GM, Schonfeld SJ, Linet MS, Sigel BS, et al. Association of chemotherapy for solid tumors with development of therapy related myelodysplastic syndrome or acute myeloid leukemia in the modern era. published online JAMA OncolDecember 20, 2018. https://doi.org/10.1001/jamaoncol.2018.5625.
[44] Bhatia S, Krailo MD, Chen Z, et al. Therapy-related myelodysplasia and acute myeloid leukaemia after Ewing sarcoma and primitive neuroectodermal tumour of bone: a report from the Children's Oncology Group. Blood 2007;109(1):46–51.
[45] Kaldor JM, Day NE, Pettersson F, et al. Leukemia following chemotherapy for ovarian cancer. N Engl J Med 1990;322(1):1–6.
[46] Travis LB, Holowaty EJ, Bergfeldt K, et al. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. N Engl J Med 1999;340(5):351–7.