Best Practice & Research Clinical Haematology 26 (2013) 309–317

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

1

The evolving challenge of therapy-related myeloid neoplasms

Jane E. Churpek, MD, Assistant Professor of Medicine [a,b,**], Richard A. Larson, MD, Professor of Medicine [a,c,*]

[a] Section of Hematology Oncology, Department of Medicine, The University of Chicago, Chicago, IL, USA
[b] Center for Clinical Cancer Genetics, The University of Chicago, Chicago, IL, USA
[c] Comprehensive Cancer Center, The University of Chicago, Chicago, IL, USA

Keywords:
therapy-related
myeloid
neoplasm
leukemia
myelodysplastic syndrome

Therapy-related myelodysplastic syndrome (t-MDS) and therapy-related acute myeloid leukemia (t-AML) are late complications of cytotoxic therapies used to treat malignant, and increasingly, non-malignant conditions. Although distinct clinical, morphologic, and genetic features can be recognized, these disorders should be seen as part of a single disease spectrum recognized by the WHO in a singular classification, therapy-related myeloid neoplasms (t-MNs). Etiologic factors for t-MNs remain elusive, but ongoing research has characterized risk factors which vary between patient subgroups and exposures. Agents that damage DNA directly, interfere with DNA repair, and suppress the immune system's ability to detect malignant cells increase the risk of t-MNs. As in primary MDS and *de novo* AML, prognosis and treatment strategies rely on patient characteristics as well as cytogenetics. However, the overall outcome for patients with t-MNs remains poor. Here we review our current understanding of t-MNs as they are most often encountered by the practicing clinician.

Introduction

Therapy-related myeloid neoplasms (t-MNs) are an increasingly common and often lethal late complication of cytotoxic treatment for a primary cancer or a non-malignant disease. Although t-MNs

* Corresponding author. The University of Chicago, Section of Hematology Oncology, 5841 S. Maryland Avenue, MC 2115, Chicago, IL 60637, USA. Tel.: +1 773 702 6783; Fax: +1 773 702 3002.
** Corresponding author. The University of Chicago, Section of Hematology Oncology, 5841 S. Maryland Ave., MC 2115, Chicago, IL 60637, USA. Tel.: +1 773 834 1076; Fax: +1 773 702 9268.
E-mail addresses: jchurpek@medicine.bsd.uchicago.edu (J.E. Churpek), rlarson@medicine.bsd.uchicago.edu (R.A. Larson).

1521-6926/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.beha.2013.09.001

can be subdivided into therapy-related myelodysplastic syndrome (t-MDS), therapy-related acute myeloid leukemia (t-AML), and therapy-related myelodysplastic/myeloproliferative neoplasms based on disease parameters, all of these presentations are best considered to be within the spectrum of a single disease entity [1]. At present, etiologic factors remain elusive, but ongoing research is beginning to characterize risk factors for t-MNs which are vary between individual patient subgroups and exposures. As in *de novo* AML, prognosis and treatment strategies are based on patient characteristics as well as on cytogenetics. However, the overall outcome for the majority of patients with t-MNs remains poor [2–4]. Here we review our current understanding of t-MNs as they are most often encountered by the practicing clinician.

Definition and recognized subgroups

t-MNs have been defined by the World Health Organization (WHO) as myeloid neoplasms, including the spectrum of MDS, AML, and overlap myelodysplastic/myeloproliferative neoplasms, occurring at any time after exposure to DNA damaging agents in a patient who previously had a non-myeloid disorder [1]. Thus, patients relapsing with MDS after treatment for AML or a chronic myeloproliferative neoplasm, for example, are not included. Patients exposed to environmental hematotoxins such as benzene are also not included although the mechanisms of malignant transformation may be similar to those active in t-MN. The implicated cytotoxic exposures include traditional cytotoxic chemotherapeutic agents and radiation therapy, given mostly for malignant but also for some non-malignant diseases. Classically, two specific subtypes of t-MNs are recognized in association with different classes of cytotoxic exposures. The first subtype, associated with exposure to alkylating agents (such as cyclophosphamide, melphalan, mechlorethamine, or nitrosureas), is characterized by a longer latency of 3 to greater than 10 years, a preceding myelodysplastic phase, deletions or loss of chromosomes 5 or 7 or both (sometimes as part of complex karyotypes), and frequent somatic loss of *TP53* [5]. Both radiation therapy and antimetabolites (such as azathioprine) are also associated with t-MN, usually with characteristics similar to those arising after alkylating agents [5,6]. The second subtype, associated with exposure to topoisomerase-II inhibitors (such as etoposide, doxorubicin, or mitoxantrone), is characterized by a shorter latency of only a few months up to about 3 years, often lacks a preceding myelodysplastic phase, presents with acute leukemia, and features balanced chromosomal rearrangements especially involving chromosome bands 11q23 or 21q22 [5]. Of note, therapy-related acute promyelocytic leukemia with a typical t(15;17) has been reported in patients treated with mitoxantrone for multiple sclerosis [7]. With the increasing use of multiagent chemotherapeutic regimens for many malignancies, many cancer survivors have been exposed to several mechanistic classes or modalities of cytotoxic agents, making it more difficult to implicate a single causative agent or the time course over which the critical DNA damage occurred.

Epidemiology

At present, t-MNs account for 10–20% of all malignant myeloid diagnoses [1]. With current estimates of 13.7 million cancer survivors in the United States alone and expectations of 18 million survivors by 2022 [8], the population of individuals at risk is growing, and a continued increase in the incidence of t-MNs is expected. The development of t-MNs appears to be independent of the specific primary disease for which cytotoxic therapy was prescribed. Thus, in the setting of prior cytotoxic therapy, these myeloid neoplasms are best labeled “therapy-related” and not “secondary leukemia” or “second malignancies”.

Efforts to understand the risk factors for the development of t-MN have identified various populations at risk among patients treated for different neoplastic and non-neoplastic diseases as well as among patients with the same primary disease but who received different treatment regimens. Cases of t-MNs are seen among survivors of both solid tumors as well as hematologic malignancies [2,3]. The largest published series of t-MN cases at a single center was published by our group at the University of Chicago [3]. It included 306 individuals diagnosed with t-MN between the early 1970s through 2001; 55% of patients had a prior hematologic malignancy, 38% had a prior solid tumor, and 6% had been treated for non-malignant diseases. Among these, individuals with prior Hodgkin lymphoma (45%) and