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No potential conflicts of interest relevant to this article were reported.

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## Therapy-related myeloid neoplasms after transcatheter arterial chemoembolization for hepatocellular carcinoma

**TO THE EDITOR:** Patients who are exposed to DNA-damaging agents, such as the chemicals used in cytotoxic chemotherapy and radiation therapy, are at risk of developing therapy-related myeloid neoplasms (t-MNs). Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths, especially in East Asia. Transarterial chemoembolization (TACE) is widely used in patients with HCC, wherein anthracycline or platinum-based agents are infused into the liver. Herein, we describe 8 cases of t-MNs that occurred after TACE in 2 tertiary institutes in Korea. A retrospective medical record review was performed for 8 patients: all were male; 4 had acute myeloid leukemia (AML), 1 had acute promyelocytic leukemia, and 3 had myelodysplastic syndromes (MDS). The TACE procedure was performed 2-14 times, and the cumulative dose of doxorubicin ranged from 60 to 700 mg. The median time for t-MN development after TACE was 36.4 months (range, 16.8-64.1 mo). Two patients were treated with sorafenib and 1 patient received radiation therapy. Patients who developed t-MNs after TACE for HCC generally showed a dismal prognosis; no

patient with AML survived for more than 6 months and only 1 patient with MDS survived for 29 months after showing a good response to decitabine. We describe a new entity of t-MNs in patients who received TACE for HCC, an under-evaluated and under-reported disease that warrants further investigation. Considering its poor prognosis, early detection and optimal management are needed to improve treatment outcomes.

### INTRODUCTION

Therapy-related myeloid neoplasms (t-MNs) are a subgroup of acute myeloid leukemia (AML) in the revised 2017 World Health Organization (WHO) classification. The neoplasms include therapy-related myelodysplastic syndrome (t-MDS), therapy-related myelodysplastic syndrome/myeloproliferative neoplasm (t-MDS/MPN), and therapy-related acute myeloid leukemia (t-AML) in patients who are exposed to cytotoxic or radiation therapy for an unrelated malignancy or autoimmune disease [1]. The pathogenesis of t-MN has not been completely elucidated. Historically, t-MN development has been considered a consequence of DNA damage induced by cytotoxic therapy or the induction of genome instability in normal hematopoietic stem cells. Recently, it has been argued that intrinsic factors, including preexisting hematopoietic cell clones or inherited mutations in cancer-associated genes, may play an important role in the pathogenesis of t-MNs [2].

There are several clinical subsets of t-MNs that correlate with the nature of prior therapy. The most common subtype (in ~70% of patients) develops after treatment with alkylating agents, such as cyclophosphamide, melphalan, platinum agents, or radiotherapy, for which the latency period (the interval between treatment and disease development) is 5-10 years. It is characterized by unbalanced aberrations of chromosomes 5 and 7 and/or a complex karyotype and is often preceded by MDS. The second-most common subtype develops after the use of topoisomerase II (TOP II) inhibitors such as anthracycline drugs or etoposide. This subtype has a shorter latency period (2-3 yr) without any preceding MDS and is frequently associated with *KMT2A/MLL* gene rearrangements [3].

T-MNs account for approximately 7-10% of all AML cases [4, 5], and the incidence is expected to increase because of increasing cancer survivorship. The most common preceding malignancies are breast cancer, lymphoma, and prostate cancer [2]. Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed cancers and is a leading cause of cancer-related deaths, especially in East Asia; however, its implication has not been studied in t-MN. Transarterial chemoembolization (TACE) is a widely used therapeutic modality in HCC patients, and during this procedure, anthracycline or platinum-based agents are infused into the liver. Given the high incidence of HCC and the frequent use of TACE, we examined 8 cases of t-MNs that developed after TACE for HCC in two tertiary institutes in Korea.

## MATERIALS AND METHODS

Patients diagnosed with t-MNs after receiving TACE for HCC between 2011 and 2019 were included in the analysis. The inclusion criteria were as follows: 1) prior history of receiving TACE for HCC and 2) diagnosis of t-MNs (t-AML, t-MDS, or t-MDS/MPN) based on the revised WHO classification of myeloid neoplasms and acute leukemia. From patients' medical records, data of age, sex, cytogenetics, complete blood count, prior treatments for HCC, treatments for t-MNs, and survival outcomes were collected.

Risk stratification was performed according to the criteria for the relevant disease [6-8]. Overall survival (OS) was calculated using the Kaplan-Meier method from the date of diagnosis of t-MN to the date of death by any cause. In patients with AML, complete remission (CR) was defined as follows [9]: normal values for absolute neutrophil count ( $>1.0 \times 10^9/L$ ) and platelet count ( $>100 \times 10^9/L$ ) and independence from red blood cell transfusion; blast cells  $<5\%$ , no clusters or collection of blasts, and an absence of Auer rods on bone marrow examination; and absence of extramedullary leukemia. In patients with MDS, response was defined based on the International Working Group response criteria [10]. Data analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The need for informed consent was waived by the institutional review boards of each institute (Chung-Ang University Hospital, 1907-028-19321; Samsung Medical Center, 2019-04-008).

## RESULTS

### Patient characteristics at the time of HCC diagnosis and treatment

Eight patients diagnosed with t-MN were identified after receiving TACE for HCC. At the time of HCC diagnosis,

their median age was 60 years (range, 45-67 yr), and all patients were male. Hepatitis B virus was the most prevalent etiology (N=4, 50%), followed by alcohol intake (N=3, 37.5%) and cryptogenic factors (N=1, 12.5%). Splenomegaly was present in 4 patients (50%). TACE was performed at a median of 4 cycles (range, 2-14 cycles), and all procedures were performed with doxorubicin at a median cumulative dose of 190 mg (range, 60-700 mg). Throughout the treatment period for HCC, 1 patient (12.5%) had received radiation therapy on the hepatic area, and 2 patients (25%) had received sorafenib for systemic disease in addition to TACE. The details are listed in Table 1.

### Patient characteristics at the time of t-MN diagnosis and treatment outcomes

In this series, t-MNs were diagnosed after a median time of 36.4 months (range, 16.8-64.1 mo) at a median age of 63 years (range, 45-72 yr). Among 8 patients with t-MNs, 5 had t-AMLs (including 1 acute promyelocytic leukemia or APL) and 3 had t-MDS. All patients had leukopenia rather than leukocytosis, and 5 patients had splenomegaly. In 5 patients with leukemia, the bone marrow blast percentage ranged from 21.5% to 93.4%. Three patients—1 patient with APL and 2 patients with AML—demonstrated recurrent cytogenetic abnormalities including  $inv(16)$ ,  $t(9;11)$ , and  $t(15;17)$ ; 1 patient with AML demonstrated  $del(7)$ , and the other had a complex karyotype. In the 3 patients with MDS, 2 were categorized into the intermediate-1 risk group, and the third patient with a complex karyotype was categorized into the intermediate-2 risk group according to the revised International Prognostic Scoring System classification [8].

Three patients with AML were treated with intensive chemotherapy consisting of induction treatment with idarubicin plus cytarabine, followed by consolidation treatment with cytarabine; all of them died due to multiorgan failure or sepsis during the treatment. The fourth AML patient was treated with 3 cycles of decitabine and could not achieve hematologic improvement; he died due to sepsis. One APL patient was treated with tretinoin plus idarubicin and died

**Table 1.** Characteristics at the time of HCC diagnosis and treatment course.

| Case | Age at HCC diagnosis, years | Sex  | Etiology    | N of TACE cycle (s) | Cumulative dose of doxorubicin (mg) | Use of sorafenib | Radiation therapy |
|------|-----------------------------|------|-------------|---------------------|-------------------------------------|------------------|-------------------|
| 1    | 46                          | Male | HBV         | 4                   | 80                                  | No               | No                |
| 2    | 45                          | Male | HBV         | 2                   | 60                                  | No               | No                |
| 3    | 64                          | Male | Alcohol     | 5                   | 180                                 | No               | Yes               |
| 4    | 63                          | Male | HBV         | 2                   | 100                                 | No               | No                |
| 5    | 64                          | Male | HBV         | 10                  | 500                                 | Yes              | No                |
| 6    | 58                          | Male | Alcohol     | 14                  | 700                                 | Yes              | No                |
| 7    | 54                          | Male | Alcohol     | 4                   | 200                                 | No               | No                |
| 8    | 67                          | Male | Cryptogenic | 4                   | 200                                 | No               | No                |

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

due to hepatic failure. The patient experienced massive ascites during treatment with tretinoin.

Among the 3 patients with MDS, 2 were treated with decitabine. One patient achieved CR after 6 cycles of decitabine and received 3 more cycles of decitabine. However, this patient stopped decitabine due to deterioration of liver function and died due to HCC progression. One patient died due to sepsis after 2 cycles of decitabine treatment. The remaining 1 patient did not receive any hypomethylating agent and was treated with transfusion and erythropoietin. Patient outcomes are listed in **Table 2**.

**DISCUSSION**

Currently, any myeloid neoplasm that arises in a patient with a history of chemotherapy or radiation therapy is defined as a t-MN. As this definition is neither quantitative nor qualitative, t-MNs cannot be distinguished from de novo

myeloid neoplasms, especially in the case of an elderly patient who had been treated with a relatively lower dose of chemotherapeutic agents or radiation therapy. Moreover, there are no genetic features, such as unbalanced aberrations of 5 or 7, complex karyotype, or *TP53* mutation, to distinguish a t-MN from a de novo myeloid neoplasm [11].

The cumulative risk of developing t-MN is relatively low [2]. The prerequisites for primary cancer include a long life expectancy and a higher chance of being cured with chemotherapy. The most common primary cancers are breast cancer, non-Hodgkin’s lymphoma, prostate cancer, and Hodgkin’s lymphoma [2]. However, HCC is a highly fatal malignancy in which chemotherapy has a limited role. There have been very few reports describing HCC as a primary cancer of t-MN. In a Japanese report, 77-year-old male patients who had been treated with TACE with epirubicin for HCC developed APL 2 years after the first TACE

**Table 2.** Characteristics at the time of t-MN diagnosis and treatment outcomes.

| Case | Diagnosis | Age at t-MN diagnosis, years | Child-Pugh class | Latency period <sup>a)</sup> | ECOG PS score | Bone marrow blast (%) | Splenomegaly | Cytogenetics risk group                                    | Treatment course   | OS (mo) |
|------|-----------|------------------------------|------------------|------------------------------|---------------|-----------------------|--------------|--|--|---------|
| 1    | t-AML     | 52                           | A                | 52.3                         | 2             | 75                    | Yes          | inv(16)<br>Favorable                                       | Died of multiorgan failure immediately after starting intensive chemotherapy   | 0.5     |
| 2    | t-AML     | 45                           | A                | 36.4                         | 1             | 21.5                  | No           | del(7)<br>Poor   | Although the patient achieved CR after induction treatment, he died of sepsis after 2 cycles of consolidation treatment  | 5.7     |
| 3    | t-AML     | 65                           | A                | 16.8                         | 1             | 84                    | Yes          | t(9;11)<br>Intermediate                                    | Although the patient achieved CR after induction treatment, he died of sepsis after 1 cycle of consolidation treatment   | 2.9     |
| 4    | t-APL     | 65                           | B                | 22.1                         | 2             | 93.4                  | Yes          | t(15;17)<br>Low  | Died of hepatic failure during induction treatment with idarubicin+tretinoin   | 0.9     |
| 5    | t-AML     | 69                           | A                | 62.4                         | 2             | 39                    | Yes          | Complex karyotype <sup>b)</sup><br>Poor                    | Died of sepsis after 3 cycles of decitabine treatment  | 2.9     |
| 6    | t-MDS     | 62                           | A                | 28.0                         | 1             | 3.2                   | No           | del(20)<br>Intermediate (IPSS-R 3.5)                       | The patient achieved CR after 6 cycles of decitabine and received 3 more cycles of decitabine. The patient stopped treatment due to liver dysfunction and died of HCC progression. | 29.0    |
| 7    | t-MDS     | 59                           | B                | 55.7                         | 3             | 1.2                   | No           | Complex karyotype <sup>c)</sup><br>Very high (IPSS-R 10.0) | Died of sepsis after 2 cycles of decitabine treatment  | 2.8     |
| 8    | t-MDS     | 72                           | A                | 64.1                         | 1             | 1.2                   | Yes          | -Y<br>Low (IPSS-R 2.0)                                     | The only case to survive on erythropoietin   | 11.5    |

<sup>a)</sup>From the date of the first TACE to the date of diagnosis of t-MN (mo). <sup>b)</sup>46,XY,inv(16)(p13.1q22)[3]/46,sl,del(2)(p13p23)[8]/46,sl,der(3)del(3)(p13p21)inv(3)(q12q23)[7]/46,XY[10]. <sup>c)</sup>45,XY,del(5)(q22q32),der(11)t(11;?;20)(q23;?;q11.2),-20,-21,+mar1[11]/45,idem,+der(11)del(p11.2)t(11;?;20),-18[11]/45,idem,t(2;21)(q11.2;q22),+21,-mar1[4]/46,idem,t(1;21)(p13;q22),+21,-mar1,+mar2[3]/46,XY[1].  
Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; MDS, myelodysplastic syndrome; OS, overall survival; TACE, transcatheter arterial chemoembolization; t-MN, therapy-related myeloid neoplasm.

[12]. A Korean single-center study reported 4 patients with t-MN development from HCC [13]. In the current study, we describe the clinicopathological features of 8 patients who were diagnosed with t-MN after receiving TACE with doxorubicin for HCC. The patients' median age was 63 years (range, 45–72 yr) and the median latency period was 36.4 months (range, 16.8–64.1 mo), which are comparable to those of patients developing t-MN after being exposed to TOP II inhibitors. In addition, most of the cytogenetic features of our patients have been reported previously in patients with t-MN from other malignancies. Although it remains unclear whether or not the t-MNs of these 8 patients were profoundly affected by TACE, the diagnosis of t-MNs was made on the basis of the WHO classification. The exact role of TACE for HCC in t-MN has rarely been discussed in literature. Inherited genetic cancer susceptibility or clonal selection may explain the sequential development of HCC and AML, although they have not been described before. Although systemic leakage of doxorubicin may occur during TACE, the leakage amount seems to be negligible. One hypothesis is that hematopoietic stem cells residing in the liver [14] could have been affected by the anthracycline drug during TACE and could have evolved to become leukemic stem cells.

Patients with t-MNs have a worse prognosis compared to patients with de novo AML, as t-MNs are associated with a higher rate of treatment-related mortality [15] as well as short relapse-free and overall survival [2]. Although the outcomes largely depend on the cytogenetic risk group, patients with t-MN often have poor cytogenetics, and their life expectancy remains poor. In our study, none of the patients with t-AML survived for more than 6 months, and the survival of the t-MDS patients was also dismally low except in 1 case. This poor survival is partially explained by the patients' susceptibility to infection as well as liver dysfunction.

t-MN from HCC may be an under-recognized category for 2 reasons. First, even if a patient presents with progressive pancytopenia, physicians may assume that this phenomenon is a consequence of splenic sequestration or sorafenib treatment. Second, advanced age or poor prognosis of advanced, incurable HCC can negate the necessity of bone marrow evaluation.

In conclusion, we describe a rare entity of t-MNs in patients who underwent TACE for HCC—an under-evaluated and under-reported phenomenon. At the same time, the mechanism, time- and dose-dependent chemotherapeutic effects on t-MNs, and relevant cytogenetic aberrations should be further explored. As HCC is more prevalent in Asia, further investigation is required to better characterize this disease and facilitate its early detection and optimal management considering its poor prognosis.

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