

# Therapy-related acute myeloid leukemia: A case series

JIE YANG and BAOAN CHEN

Department of Hematology and Oncology, Zhongda Hospital, School of Medicine,  
Southeast University, Nanjing, Jiangsu 210009, P.R. China

Received January 4, 2022; Accepted March 31, 2022

DOI: 10.3892/ol.2022.13291

**Abstract.** Patients with primary cancer receiving chemotherapy and/or radiotherapy may develop therapy-related acute leukemia (t-AL). Therapy-related acute myeloid leukemia (t-AML) accounts for the majority of these cases and is frequently associated with a variety of cytogenetic and molecular abnormalities. The aim of the present study was to explore the clinical characteristics, treatments and prognosis of patients with t-AML. A total of 272 cases of AML treated at our institution between 2016 and 2020 were reviewed, among which nine cases of t-AML were identified for analysis. All patients had received alkylating or topoisomerase II inhibitor chemotherapy drugs for primary cancer treatment and three patients had received radiotherapy. A total of nine patients had been administered recombinant human granulocyte colony-stimulating factor (G-CSF). The median latency period for the nine patients with t-AML was 25 months (range, 10-240 months). The molecular cytogenetic abnormalities included t(15:17)(q22;q21), inv(16)(p13q22), del(5)(q22), CBFB/MYH11(+), FLT3(+), NARS(+), IDH(+), TET2(+), and TP53(+). Out of nine patients with t-AML, eight received chemotherapy, two of whom underwent HSCT. The median survival time of the nine patients with t-AML was 10 months and the 2-year-survival rate was 44.4%. Greater clarity around the diagnosis and treatment is required to improve the outcomes of patients with t-AML.

## Introduction

The prevalence of therapy-related acute leukemia (t-AL) is increasing rapidly, primarily due to widespread use of cytotoxic therapy, including chemotherapy and/or radiation therapy for prior cancer that significantly prolonged survival of cancer patients (1). According to the available research

results, most t-AL cases are of myeloid lineage, with distinct clinical and pathological features. Therapy-related myelodysplastic syndrome and therapy-related acute myeloid leukemia (t-AML) have secured a place in the World Health Organization (WHO) classification of hematopoietic neoplasms as separate entities (2), accounting for up to 10-20% of all AL cases (3). Compared with *de novo* AML, the prognosis of t-AML has always been poor, with a higher cytogenetic abnormal risk and shorter survival time (4-6). Long-term damage from previous cytotoxic drug treatments and primary immune disorders generally result in resistance to high-intensity chemotherapy drugs (7). Moreover, the poor prognosis observed in patients with t-AML is dependent of older age at presentation and comorbidities (8). These t-AML patients are generally insensitive to high-intensity chemotherapy agents due to long-term damage from prior cytotoxic drug therapy and the presence of immune disorders (4). As the current treatment of t-AML thus remains challenging, the aim of the present study was to investigate the clinicopathological features of nine cases of t-AML treated at our department between 2016 and 2020, and to provide a reference for the current clinical treatment of t-AML.

## Materials and methods

**Patients.** A total of 272 consecutive AML cases, which were treated at the Department of Hematology and Oncology of Zhongda Hospital (Jiangsu, China) between January 2016 and January 2020, were reviewed. The WHO criteria published in 2016 (2) were followed to diagnose AML, and a bone marrow (BM) biopsy was evaluated by a professional haemato-pathologist. The cases of t-AML were identified based on their exposure to chemotherapy and/or radiotherapy for primary cancer treatment, regardless of the latency period. Clinical data pertaining to the patients were obtained from their medical records.

**Cytogenetic and molecular analysis.** BM aspirates were collected from all the patients with t-AML at the time of admission. Cytogenetic analysis was conducted using conventional G-banding technology and fluorescence *in situ* hybridization. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (9). A mutational analysis of the DNA extracted from each aspirate was performed using next-generation sequencing on 34 genes frequently mutated in AML (10).

---

**Correspondence to:** Professor Baoan Chen, Department of Hematology and Oncology, Zhongda Hospital, School of Medicine, Southeast University, 87 Dingjiaqiao, Gulou District, Nanjing, Jiangsu 210009, P.R. China  
E-mail: cba8888@hotmail.com

**Key words:** therapy-related acute myeloid leukemia, chemotherapy, radiotherapy, treatment, prognosis

Table I. Primary tumor status of the patients with t-AML (n=13).

Patient number	Sex	Age, years	Diagnosis	Chemotherapy	Radiotherapy	G-CSF application
1	Female	39	Breast cancer (T2N2M0)	ECT x 6 + anastrozole	No	Yes
2	Female	58	Breast cancer (T2N1M0)	ECT x 6	Yes	Yes
3	Male	66	Gastric cancer (T1N2M0)	XELOX	No	Yes
4	Female	51	Breast cancer (T2N0M0)	ECT x 6	No	Yes
5	Female	79	Intestinal cancer (T2N2M0)	NA	No	Yes
6	Female	44	Breast cancer (T2N0M0)	CMF x 6	Yes	Yes
7	Female	62	Breast cancer (T2N2M0)	CMF x 6	Yes	Yes
8	Male	43	Intestinal cancer (T2N2M0)	FOLFIRI	No	Yes
9	Male	73	Gastric cancer (T3N1M0)	XELOX	No	Yes

ECT, epirubicin + cyclophosphamide + docetaxel; CMF, cyclophosphamide + methotrexate + 5-fluorouracil; XELOX, oxaliplatin + capecitabine; FOLFIRI, Irinotecan + leucovorin + 5-fluorouracil; G-CSF, granulocyte colony stimulating factor; NA, not applicable.

**Data collection and analysis.** The patients' baseline clinical data, postoperative chemotherapy and/or radiotherapy regimens, and outcomes of primary cancer were collected. The baseline clinical and molecular characteristics, the time between primary cancer and t-AML, outcomes and the intensity of therapy of the nine patients with t-AML were recorded. Response criteria of t-AML therapy, including complete remission (CR), CR with incomplete hematologic recovery, morphological leukemia-free state and partial remission (PR), were defined according to the 2017 European LeukemiaNet criteria (11) (the patients of the present study did not meet these criteria).

## Results

**Patient characteristics.** A total of nine patients with t-AML were identified, including three males and six females. The primary cancer types included breast cancer and gastrointestinal cancer. All the patients were engaged in general occupations and had no history of exposure to radioactive or toxic substances at the time of the analysis. The median age at diagnosis of primary cancer was 63 years (range, 41-81 years).

**Primary cancer treatment.** Surgical treatment was performed on all nine patients, and diagnosis of primary cancer was confirmed by postoperative pathological examination. The relevant data on the primary tumor status of the nine patients with t-AML are detailed in Table I.

Postoperative combination chemotherapy regimens of the five breast cancer cases involved epirubicin, cyclophosphamide (CTX), docetaxel, methotrexate and 5-fluorouracil. All of the breast cancer patients were treated with CTX.

The other 4 cases were gastrointestinal tumors. Excluding case number 5 for which the relevant data were not available due to their long latency period, the remaining 3 patients with gastrointestinal tumor received standard chemotherapy regimens including XELOX (oxaliplatin + capecitabine), and FOLFIRI (irinotecan + leucovorin + 5-fluorouracil) with no radiotherapy.

All nine patients used recombinant human granulocyte colony-stimulating factor (G-CSF) during chemotherapy.

**t-AML characteristics.** According to the 2016 WHO diagnostic classification criteria, 3 cases of AML with maturation (M2), 2 cases of acute promyelocytic leukemia (M3), 2 cases of acute myelomonocytic leukemia (M4), and 2 cases of acute monocytic leukemia (M5) were included in the case series. The median latency time from the start of treatment of primary cancer to the onset of t-AML of the 9 patients was 25 months (range, 10-240 months). The median overall survival time of the nine patients with t-AML was 10 months, and four patients (44.4%) survived for >2 years. Cytogenetic or molecular abnormalities were exhibited by seven cases, including two cases of t(15:17) (q22;q21), one case of inv(16)(p13q22), one case of del(5)(q22), two cases of CBFB/MYH11(+), two cases of FLT3(+), one case of NARS(+), one case of IDH(+), one case of TET2(+), and one case of TP53(+). Only one patient showed normal cytogenetic and molecular genetic profiles. All the patients' characteristics are described in Table II.

**Treatment and prognosis of t-AML.** All patients received conventional induced remission and salvage therapy, and 2 eligible patients received HSCT. Azacitidine + homoharringtonine + cytarabine + G-CSF therapy was administered to two out of three patients with M2 and they achieved CR (patient number 6, Table II) and PR (patient number 8, Table II). The patient who achieved CR is still alive, whereas the PR patient died of disease progression. The third M2 patient (patient number 9, Table II) died without receiving any therapy because of a severe lung infection caused by weak immunity. All the M3 patients (patient numbers 3 and 7) achieved CR with all-trans retinoic acid + arsenous acid (ATRA + ATO) remission induction and ATO consolidation chemotherapy. At the time of this analysis, these patients were still under regular follow-up. The 2 M4 patients received mitoxantrone + cytarabine (patient number 1) and medium-dose cytarabine (patient number 2) chemotherapy, respectively. Subsequently, autologous (auto) HSCT was undertaken on patient number 1 and the patient was still alive at the time of this analysis. CR was not achieved by patient number 2 who subsequently died of disease progression. The 2 M5 patients received idarubicin (number 4) and decitabine (number 5) chemotherapy, respectively. After having achieved CR, allogeneic (allo)

Table II. Characteristics, treatment and outcome of nine patients with therapy-related acute myeloid leukemia.

Patient number	AML type	Incubation time (months)	WBC (x10 <sup>9</sup> /l)	Bone marrow blasts (%)	Cytogenetic and molecular abnormalities <sup>a</sup>	Treatment	Outcome	OS time (months)
1	M4	21	135.08	85.2	46, XX, inv(16)(p13q22)[15]/46, XX[5], CBFβ/MYH11(+)	MA (2 courses of chemotherapy) CR + auto-HSCT	Survival	48
2	M4	20	35.48	70	46, XX; NRAS, CBFβ/MYH11(+)	MD-Ara-C (2 courses of chemotherapy) PR	Death (disease progression)	10
3	M3	60	1.3	12	46, XY, t(15:17)(q22;q21)(9)/46, XY[1]	ATRA+ATO (1 courses of chemotherapy) CR + ATO (10 courses of chemotherapy)	Survival	31
4	M5	10	2.5	63	46, XX	IDA (2 courses of chemotherapy) CR + allo-HSCT	Survival	25
5	M5	14	3	20.8	46, XX, del(5)(q22)[18]/46, XX[2]	DAC (2 courses of chemotherapy) PR	Death (disease progression; severe lung infection)	4
6	M2	60	1.99	32	46, XX; IDH, TET2 (+)	AZA+HAG (6 courses of chemotherapy) CR	Survival	2
7	M3	25	3.7	8	46, XX; t(15:17)(q22;q21)	ATRA+ATO (1 courses of chemotherapy) CR + ATO (8 courses of chemotherapy)	Survival	23
8	M2	240	1.2	36.7	46, XY; FLT3, TP53(+)	chemotherapy AZA+HAG (3 courses of chemotherapy) PR	Death (disease progression)	7
9	M2	26	10.3	92	46, XY; FLT3(+)	No	Death (severe lung infection)	1

<sup>a</sup>The number in the square brackets after XX or XY represents the number of chromosomes analyzed. Allo-HSCT, allogeneic hematopoietic stem cell transplantation; MA, mitoxantrone + cytarabine; MD-Ara-C, medium-dose cytarabine; ATRA, all-trans retinoic acid; ATO, arsenous acid; IDA, idarubicin; DAC, decitabine; AZA, azacitidine; HAG, homoharringtonine + cytarabine + granulocyte colony stimulating factor; M2, AML with maturation; M3, acute promyelocytic leukemia; M4, acute myelomonocytic leukemia; M5, acute monocytic leukemia; OS, overall survival; WBC, white blood cell.

HSCT was performed on patient number 4, while PR was achieved by patient number 5 patient who thereafter died of disease progression and severe infection. The characteristics, treatments, and outcomes of the nine patients with t-AML are listed in Table II. Relatively improved outcomes were achieved by the patients with CR who subsequently had HSCT.

## Discussion

t-AL is one of the long-term complications of patients with cancer receiving radiotherapy and/or chemotherapy/or immunosuppressive treatment (12,13). In general, t-AL is characterized by poor responsiveness to traditional therapies, rapid disease progression, and poor prognosis (14-17). Compared with the patients who do not receive chemotherapy, patients who receive high-dose chemotherapy have a significantly higher occurrence risk of t-AL (18,19). Among all t-AL cases, t-AML accounts for a high proportion, while (therapy-related acute lymphoblastic leukemia, t-ALL) is relatively rare. Furthermore, breast cancer t-AML is the most common subtype and accounts for up to 30% of all cases of t-AML (20).

Alkylating agent (such as cyclophosphamide and melphalan) and/or topoisomerase II inhibitor (such as doxorubicin, etoposide, pirarubicin, and other anthracyclines) application at high doses to achieve a certain accumulated drug dose in the body is the main cause of t-AML (21,22). In the present study, eight patients used the aforementioned types of chemotherapy drugs during their treatment.

Patients with t-AML have a relatively higher mutation frequency of IDH and TP53 (8,23). IDH gene mutation can change the epigenetics of cells, leading to histone hypermethylation, which may be an event that occurs early in t-AML (24,25). FLT3 gene mutation can also be observed in patients with t-AML, generally indicating a negative prognosis (6). In the present study, IDH, FLT3, and/or TP53 mutations were present in three cases of t-AML-M2. Of these three patients, two died of disease progression and severe infection, respectively.

Rashidi and Fisher (26) have suggested that topoisomerase II inhibitors and radiation were the most common causes of t-AML-M3. Chemotherapeutic drugs can interfere with DNA double-strands mainly by inhibiting topoisomerase II, promoting t(15;17)(q22;q21) and PML/RAR $\alpha$ , thereby inducing t-AML-M3 occurrence (27). In the present study, the reciprocal translocation t(15;17)(q22;q21) was found in t-AML-M3 patients who previously underwent radiotherapy, and the typical therapy (ATRA + ATO) showed a positive result.

The inv16 inversion is the most common chromosomal abnormality in AML-M4, including patients with t-AML, and the CBF $\beta$ /MYH11 gene fusion can also be detected (8,28). These generally indicate a better prognosis according to a previous study (28).

It has been shown that abnormalities of chromosome 5 or 7 are associated with poor prognosis in patients with t-AML (29).

With the development of neoadjuvant therapy and the continuous extension of cancer survival, the incidence of t-AL has also increased significantly. Therefore, by ensuring

appropriate treatment of the primary cancer, occurrence of such of therapy-related malignancies may be avoided. Furthermore, in the treatment of t-AML, fully evaluated and individualized treatment should be developed. Monoclonal antibodies, targeted therapies, and HSCT are promising treatments for t-AML (12,30). Since this study is a single-center study, the number of included cases is small and not highly representative. Existing results can only represent the situation of a small number of patients in limited areas to a certain extent. Multi-center cooperation is urgent to be carried out to expand the number of cases and involved region. With more research results and further analysis included, additional findings will further guide the clinical diagnosis and treatment to improve the outcomes of patients with t-AL.

## Acknowledgements

Not applicable.

## Funding

This study was supported by Natural Science Foundation of Jiangsu Province for Youth (BK20180372), Jiangsu Provincial Medical Youth Talent (grant no. QNRC2016812), and Key Medical of Jiangsu Province (grant no. ZDXKB2016020).

## Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author or reasonable request.

## Authors' contributions

JY and BC were involved in the conception and design of the study. JY collected the data. JY and BC were involved in data analysis and interpretation and were involved in the writing of the manuscript. JY and BC confirmed the authenticity of all the raw data. Both authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

The patients and their families were informed that data from the case would be submitted for publication and gave consent for the academic use of clinical information.

## Competing interests

The authors declare that they have no competing interests.

## References

1. Morton LM, Doros GM, Schonfeld SJ, Linet MS, Sigel BS, Lam CJK, Tucker MA and Curtis RE: Association of chemotherapy for solid tumors with development of therapy-related myelodysplastic syndrome or acute myeloid leukemia in the modern era. *JAMA Oncol* 5: 318-325, 2019.

2. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M and Vardiman JW: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 127: 2391-2405, 2016.
3. Hulegårdh E, Nilsson C, Lazarevic V, Garelus H, Antunovic P, Rangert Derolf Å, Möllgård L, Ugglä B, Wennström L, Wahlin A, *et al*: Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: A report from the Swedish acute leukemia registry. *Am J Hematol* 90: 208-214, 2015.
4. Cheung E, Perissinotti AJ, Bixby DL, Burke PW, Pettit KM, Benitez LL, Brown J, Scappaticci GB and Marini BL: The leukemia strikes back: A review of pathogenesis and treatment of secondary AML. *Ann Hematol* 98: 541-559, 2019.
5. Granfeldt Østgård LS, Medeiros BC, Sengeløv H, Nørgaard M, Andersen MK, Dufva IH, Friis LS, Kjeldsen E, Marcher CW, Preiss B, *et al*: Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: A national population-based cohort study. *J Clin Oncol* 33: 3641-3649, 2015.
6. Samra B, Richard-Carpentier G, Kadia TM, Ravandi F, Daver N, DiNardo CD, Issa GC, Bose P, Konopleva MY, Yilmaz M, *et al*: Characteristics and outcomes of patients with therapy-related acute myeloid leukemia with normal karyotype. *Blood Cancer J* 10: 47, 2020.
7. Kern W, Haferlach T, Schnittger S, Hiddemann W and Schoch C: Prognosis in therapy-related acute myeloid leukemia and impact of karyotype. *J Clin Oncol* 22: 2510-2511, 2004.
8. Cleven AH, Nardi V, Ok CY, Goswami M, Dal Cin P, Zheng Z, Iafrate AJ, Abdul Hamid MA, Wang SA and Hasserjian RP: High p53 protein expression in therapy-related myeloid neoplasms is associated with adverse karyotype and poor outcome. *Mod Pathol* 28: 552-563, 2015.
9. Liehr T: International system for human cytogenetic or cytogenomic nomenclature (ISCN): Some thoughts. *Cytogenet Genome Res* 161: 223-224, 2021.
10. Eisfeld AK, Mrózek K, Kohlschmidt J, Nicolet D, Orwick S, Walker CJ, Kroll KW, Blachly JS, Carroll AJ, Koltz JE, *et al*: The mutational oncoprint of recurrent cytogenetic abnormalities in adult patients with de novo acute myeloid leukemia. *Leukemia* 31: 2211-2218, 2017.
11. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, Dombret H, Ebert BL, Fenaux P, Larson RA, *et al*: Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 129: 424-447, 2017.
12. Maung SW, Burke C, Hayde J, Walshe J, McDermott R, Desmond R, McHugh J and Enright H: A review of therapy-related myelodysplastic syndromes and acute myeloid leukaemia (t-MDS/AML) in Irish patients: A single centre experience. *Hematology* 22: 341-346, 2017.
13. Ossenkoppele G and Montesinos P: Challenges in the diagnosis and treatment of secondary acute myeloid leukemia. *Crit Rev Oncol Hematol* 138: 6-13, 2019.
14. McNerney ME, Godley LA and Le Beau MM: Therapy-related myeloid neoplasms: When genetics and environment collide. *Nat Rev Cancer* 17: 513-527, 2017.
15. Vicente-Ayuso MDC, Garcia-Roa M, González-Fernández A, Álvarez-Carmona AM, Benavente-Cuesta C, Mateo-Morales M, Pérez-López C, Peña-Cortijo A, Zarzuela MP, Gutiérrez L and Martínez-Martínez R: Therapy-related myeloid neoplasms as a concerning complication in acute promyelocytic leukemia. *Hematol Rep* 9: 7204, 2017.
16. Thakral B and Muzzafar T: Diagnosing therapy-related acute myeloid leukemia with 8% blasts in bone marrow with concomitant plasma cell myeloma. *Blood* 130: 231, 2017.
17. Menghrajani K, Zhang Y, Famulare C, Devlin SM and Tallman MS: Acute myeloid leukemia with 11q23 rearrangements: A study of therapy-related disease and therapeutic outcomes. *Leuk Res* 98: 106453, 2020.
18. Lindsley RC, Mar BG, Mazzola E, Grauman PV, Shareef S, Allen SL, Pigneux A, Wetzler M, Stuart RK, Erba HP, *et al*: Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood* 125: 1367-1376, 2015.
19. Higgins A and Shah MV: Genetic and genomic landscape of secondary and therapy-related acute myeloid leukemia. *Genes (Basel)* 11: 749, 2020.
20. Renella R, Verkooijen HM, Fioretta G, Vlastos G, Kurtz J, Sappino AP, Schäfer P, Neyroud-Caspar I and Bouchardy C: Increased risk of acute myeloid leukaemia after treatment for breast cancer. *Breast* 15: 614-619, 2006.
21. Wong TN, Ramsingh G, Young AL, Miller CA, Touma W, Welch JS, Lamprecht TL, Shen D, Hundal J, Fulton RS, *et al*: Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. *Nature* 518: 552-555, 2015.
22. Dayyani F, Kantarjian H, O'Brien S, Pierce S, Jones D, Faderl S, Garcia-Manero G, Cortes J and Ravandi F: Outcome of therapy-related acute promyelocytic leukemia with or without arsenic trioxide as a component of frontline therapy. *Cancer* 117: 110-115, 2011.
23. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, Stone RM, DeAngelo DJ, Levine RL, Flinn IW, *et al*: Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood* 130: 722-731, 2017.
24. Nishiyama T, Ishikawa Y, Kawashima N, Akashi A, Adachi Y, Hattori H, Ushijima Y and Kiyoi H: Mutation analysis of therapy-related myeloid neoplasms. *Cancer Genet* 222-223: 38-45, 2018.
25. Imagawa J, Harada Y, Shimomura T, Tanaka H, Okikawa Y, Hyodo H, Kimura A and Harada H: Clinical and genetic features of therapy-related myeloid neoplasms after chemotherapy for acute promyelocytic leukemia. *Blood* 116: 6018-6022, 2010.
26. Rashidi A and Fisher SI: Therapy-related acute promyelocytic leukemia: A systematic review. *Med Oncol* 30: 625, 2013.
27. Joannides M, Mays AN, Mistry AR, Hasan SK, Reiter A, Wiemels JL, Felix CA, Coco FL, Osheroff N, Solomon E and Grimwade D: Molecular pathogenesis of secondary acute promyelocytic leukemia. *Mediterr J Hematol Infect Dis* 3: e2011045, 2011.
28. Dissing M, Le Beau MM and Pedersen-Bjergaard J: Inversion of chromosome 16 and uncommon rearrangements of the CBFβ and MYH11 genes in therapy-related acute myeloid leukemia: Rare events related to DNA-topoisomerase II inhibitors? *J Clin Oncol* 16: 1890-1896, 1998.
29. Imamura T, Taga T, Takagi M, Kawasaki H, Koh K, Taki T, Adachi S, Manabe A and Ishida Y: Leukemia/Lymphoma Committee; Japanese Society of Pediatric Hematology Oncology (JSPHO): Nationwide survey of therapy-related leukemia in childhood in Japan. *Int J Hematol* 108: 91-97, 2018.
30. Metafuni E, Chiusolo P, Laurenti L, Sorà F, Giammarco S, Bacigalupo A, Leone G and Sica S: Allogeneic hematopoietic stem cell transplantation in therapy-related myeloid neoplasms (t-MN) of the adult: Monocentric observational study and review of the literature. *Mediterr J Hematol Infect Dis* 10: e2018005, 2018.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.