Therapy-related leukemia/myelodysplastic syndrome in multiple myeloma

KAZUHIKO NATORI DAISUK NAGASE SUSUMU ISHIHARA AKIKO YUKITOSHI TOYODA MOTOHIRO KATO YOSINORI FUJIMOTO YASUNOBU KURAISHI HARUKA IZUMI

Division of Hematology and Oncology, Department of medicine

Toho University Medical Center Oomori Hospital

Oomori-nishi6-11-1, Oota-ku, Tokyo

Japan

natori@med.toho-u.ac.jp

Abstract

Although recent advances in combination chemotherapy, high-dose radiotherapy, and combination of chemotherapy and radiotherapy have prolonged the survival time of cancer patients, developments of therapy-related malignancy have increased. We experienced 9 cases of therapy-related leukemia/myelodysplastic syndrome (TRL/TMDS) during the treatment of multiple myeloma (MM). Of 177 MM cases treated with combination chemotherapy for induction or maintenance therapy in our department between 1988 and 2008, 9 cases were diagnosed of TRL/TMDS. There were 6 males and 3 females and the median age at the diagnosis of TRL/TMDS was 69 years (54-78yrs). All 4 cases of TRL were myelogeneous leukemia. In 5 cases of TMDS, there were 2 refractory anemia, 1refractory anemia with excess blasts(RAEB) and 2 chronic myelomonocytic leukemia(CMMoL). In 6 cases, the cumulative dose of melphalan exceeded 800 mg. The remission induction chemotherapy was performed in 3 cases and complete remission was achieved in 1 case and 2 were partial remission. In cases of TMDS, transfusion alone was performed in 2 cases, and controlling the white blood cell count alone in 3cases. Regarding the outcome, the median survival time was 6 months (follow-up period: 1-40 months). One patient have survived for more than 40 months, while 8 cases died caused of TRL or TMDS. The prevention of TRL/TMDS has become an important problem and careful long-term follow-up with periodic blood test is necessary after chemotherapy.

Key-Words chemotherapy, multiple myeloma, therapy-related leukemia, cytogenetic abnormality

1 Introduction

Chemotherapy and radiotherapy for malignant tumor can impair the host hematopoietic stem cells and lead to leukemia or myelodysplastic syndrome (MDS) which is referred to as therapy-related leukemia/MDS (TRL/MDS). Although recent

ISBN: 978-1-61804-111-1

advances in combination chemotherapy , high-dose radiotherapy, and combination of chemotherapy and radiotherapy have prolonged the survival time of cancer patients, deveropments of therapy-related malignancy have increased. In therapy for multiple myeloma (MM), combination chemotherapy, using alkylating agents as the key drug, has increased in potency. Furthermore, the duration of chemotherapy have become longer and the cumulative dose of anti-myeloma agents including alkylator increased more and more. We experienced 9 cases of TRL/TMDS during the treatment of MM.. Herein, we report these cases with a review of the literature.

2 Subjects

Of 177 MM cases treated with combination chemotherapy for induction or maintenance therapy in our department between 1988 and 2008, 9 cases were diagnosed of TRL/TMDS. We investigated the gender, age, time interval between the diagnosis of MM and TRL/TMDS, disease types of leukemia, and MDS, chrosomal analysis, and survival time in these 9 cases.

3 Results

3.1 patient backgrounds

There were 6 males and 3 females and the median age at the diagnosis of MM was 63 years (45-75). The median time to the diagnosis of TRL/TMDS from the diagnosis of MM was 8 years (1-10), and the median age at the time of diagnosis of TRL/TMDS was 69 years (54-78). Regarding the status of MM, partial remission (PR) was maintained in all but one case. TRL/TMDS was suggested because of rapid progression of anemia, thrombocytopenia, and leukopenia during outpatient treatment or follow-up. On the types of MM, there were 7 IgG,κ, 1 IgA ,κand 1 non-secretory type. (Table 1)

3.2 types of leukemia and myelodysplastic syndrome, chromosomal aberration, and total dose of anti-cancer drugs

All 4 cases of TRL were acute myelocytic leukemia (AML) and the types of AML were M2, M3, M5, and M6 according to the French-American-British(FAB) classification(Table 1) .With the exception of M3 case, abnormalities including aberration of chromosome 5 or 7 were noted (Table 2). The types of MDS were refractory anemia (RA) in 2 cases, refractory anemia with excess blasts (RAEB) in 1, and chronic myelomonocytic leukemia (CMML) in 2 according to FAB classification. Chromosomal aberrations were noted in 4 cases, and aberration of chromosome 2 and 7 was noted in 2 cases each (Table 2).

The cumulative dose of melphalan whichi is alkylating agent and one of the key agents in combination chemotherapy for MM exceeded 800 mg in 6 cases (Table 3).

3.3 treatment and outcome fot TRL/TML

The same regimen of remission induction chemotherapy as for de novo AML was performed in 3 cases and complete remission(CR) was achieved in

ISBN: 978-1-61804-111-1

1 and PR in 2, respectively. One patient underwent 3 cycles of CAG (cytosine arabinoside, aclarubicin, granulocyte-colony stimulatiing factor) therapy and achieved PR. In TMDS cases, stransfusion alone was performed in 2 cases , and controlling the white blood cell count alone in 3.

Regarding the outcome, the median survival time for all patients was 6 months (follow-up period: 1-40 months). One patient have survived for more than 40 months, while 8 cases died caused of TRL or TMDS.

4 Discussion

With the recent improvement of outcomes of various malignant tumors, we increasingly encounter the development of multiple primary neoplasms during the course of observation after treatment of the first cancer. Chemotherapy and radiotherapy for malignant tumor can impair the host hematopoietic stem cells, which may lead to the development of leukemia in some cases of multiple primary neoplasms, which is referred to as TRL. Since Rosner and Grunwald reported the first case of TRL in 1974[1], it has been reported increasingly, and its clinical and pathological features are considered to be specific among the desease of acute leukemia.

Since Alexanian et al.[2] proposed MP(melphalan, prednisolone) therapy in 1963, treatment for MM has become more intensive supported with development of granulocyte- colony stimulting factor for neutropenia or antibiotics for infection, Recently, intensive combination chemotherapy, high -dose chemotherapy supported with autologous hematopoietic stem cell transplantation and allogeneic hematopoitic stem cell transplantation with reduced intensity conditioning regimen have become common. Futhermore, because MM is considered non curable disease, physicians are reluctant to discontinue the treatment in patients who are well controlled, and the increasing of cumulative dose of anti-myeloma drugs for long-term survivors may elevate the risk of TRL/TMDS.

The pathological characteristics of TRL/TMDS are divided into 2 types based on the causative drugs. One type is observed in cases treated with alkylating agents: 1) The incidence of this type is about 90% of TRL cases, 2) MDS-like symptoms precede in 50-60% of cases, 3) the onset is 4-5 years after therapy, 4) chromosomal aberration is observed in more than 90% of cases, and half of these are accompanied by aberration of chromosome 5 or 7, 5) the disease is resistant to treatment, and 6) the prognosis is poor: with a complete remission rate of about 25% and a mean survival time of about 3-6 months. These clinical and pathological features are compatible with our cases. It has been revealed recently that interferon regulatory factor-1 (IRF-1) located at 5q31.1 exhibits an inhibitory effect on cancer growth. Alkylating agents often induce abnormalities in chromosomes 5 and 7, suggesting associations with antioncogenes in these regions[3]. Another type is associated with the administration of topoisomerase II inhibitors such as etoposide, doxorubicin, or mitoxantron. These drugs can induce the TRL within 2-3 years after treatment, without any preleukemia conditions, such as MDS, which is

ISBN: 978-1-61804-111-1

accompanied by balanced chromosomal aberration. The therapeutic outcome does not differ from that of *de novo* leukemia[4]. Upon the chromosomal analysis, translocation of 11q23 or 21q22 is noted in many cases, and the frequency of t(9;11)(p22;q23), t(6;11)(q27;q23) translocation is particularly high. Chimeric gene formation by translocation between the mixed-lineage or myeloid/lymphoid leukemia (MLL) gene located at 11q23 and the leukemia translocation (LTG) gene located on chromosome 4, 9, or 19 has been observed in patients with *de novo* leukemia and those with topoisomerase II inhibitor -induced leukemia, suggesting that the translocation is the cause of development of leukemia[5]. Balanced chromosomal aberrations previously considered to be specific to *de novo* AML, such as inv(16), t(15;17), t(8;16), and t(6;9), have also been reported, although these are rare in TRL.

The risk of alkylating agent induced TRL has been reported to be proportionate with the total dose of agents and the frequency of development is the highest in 5-6 years after administration of the drugs[6]. For melphalan and cyclophosphamide, dose-dependence has been reported[6,7]. The frequency was high in cases treated with melphalan at doses exceeding 700 mg[8], with an incidence 2-3 times higher than that induced by cyclophosphamide[6].

The annual expected incidence of *de novo* AML is reported as about 0.02%, and the occurrence of AML is likely at least 100 times higher in the patients treated with alkylating agents and it has been demonstrated statistically with etoposide administration also[7]. However, another report has shown no apparent relationship between the total dose of etopside and TRL in pediatric lymphoblastic leukemia patients treated with etoposide.

The outcome of treatment of TRL is generally poor in Japan and other countries. Kantarjian **et a**l.[9,10]reported that the CR rate is only 29%, and that the rate in cases with aberration of chromosome 5 or 7 is 13%, showing marked resistance to therapy. In the reports from western countries, the CR rate was 30-70% with a median survival time of 4-8 months, showing that the therapeutic outcome was poor in TRL which progressed through MDS[11,12], and a cure is only achieved with homologous transplantation. However, in the outcome of homologous bone marrow transplantation for secondary leukemia, the long-term survival rate was only 20%[13,14], suggesting that it is important to determine how to improve the quality of life in the management of patients with secondary leukemia including TMDS. Topoisomerase II inhibitor-induced TRL occurs without the preceding of MDS-like condition, chromosomal aberration or gene abnormality, is consistent with those findings in *de novo* AML, and the mechanism has been clarified. Therefore, the application of high dose therapy should be implemented without hesitation.

5. Conclusion

Nowadays, the prevention of TRL is one of the most important problem in cancer therapy. Appropriate use of anti-cancer drugs should be

ISBN: 978-1-61804-111-1

performed in each case, based upon the detection of minimal residual disease. Japanese case reports of TRL suggest that careful long-term follow-up is necessary after chemotherapy, and that periodic blood test could lead to discovery of the secondary cancer development.

References

1)Rosner,F&Grunwald,H. : Multiple myeloma terminating in acute leukemia : Report of 12 cases and review of the literature. Am J. Med. 57:927,1974

2)Raymond Alexanian : Treatment for Multiple Myeloma. Combination chemotherapy with ddiferent melphalan dose regimens. JAMA 208 1680-1685, 1969

3)Bolutwood J, *et al.* : Allelic loss of IRI1 in myelodysplasia and acute myeloid leukemia : retention of IRI1 on the 5q-chromosome in some patients with the 5q-syndrome. Blood 82 : 2611-2616,1993

4)Pedersen-Biergaard J.,Rowley JD. : The balanced and the unbalanced chromosome aberrations of acute myeloid leukemia may contribute differently to malignant transformation. Blood 83: 2780-2786,1994

5)Yamamoto K, et al : A reverse transcriptasepolymerase chain reaction detects heterogeneous chimeric mRNAs in leukemia with 11q23 abnormalities. Blood 83 : 2912-2921, 1994

6)Greene,MH.,et al : Melphalan may be a more potent leukemogen than cyclophosphamide. Ann.Intern. Med.,105 : 360-367,1986

7)Pedersen-Bjergaard J., *et al.* : Risk of therapy-related leukemia and preleukemia after Hodgkin's disease. Lancet,ii : 83-88,1987

8)Greene,MH.,et al : Melphalan may be a more potent leukemogen than cyclophosphamide. Ann.Intern. Med.,105 : 360-367,1986

9)Kantarijian HM. *et al.* : Therapy-related leukemia and myelodysplastic syndrome : clinical,cytogenic,and prognotic features. J.Clin. Oncol. 4 : 1748,1986

10)Kantarjian HM., *et al.* : Treatment of therapy-related leukemia and myelodysplastic syndrome. Haematol./Oncol. Clinics of North America 7 : 81-107,1993

11)Brito-Babapulle F,et al. : Clinical and laboratory features of de novo acute myeloid leukemia with trilineage myelodysplasia. Br. J. Haematol. 66 : 445-450,1987

12)Jinnai I,*et al.* Dysmegakaryopoiesis in acute leukemias : Its predominance in myelomonocytic(M4)leukemia and Implication for poor response to chemotherapy. Br.J.Haematol. 66 : 467-472,1987

13)Gyger M, *et al.* : restoration of normal hematopoiesis by bone marrow ablation and allogenic marrow transplantation in a case of Hodgkin's disease therapy-related preleukemia. Blood 61 : 1275-1277,1983

14)DeWitte T,*et al.* : Allogenetic bone marrow transplamtation for secondary leukemia and myelodysplastic syndrome : A survey by the Leukemia Working Party of the European Bone marrow Transplantation Group(EBMTG). Br. J. Haematol. 74 : 151-155,1990

Table1 Patient backgrounds

No. of cases	9
Male/Female	6/3
Med.age at diag. of MM(yrs)(range)	63(45-75)
Med. age of diag. of TRL/TMDS)(yrs)(range)	69(54-78)
Med. time to TRM/TNDS(yrs)(range)	8(1-10)
Initial symtom of TRL/TMDS	
Anemia	6
Infection	1
abnormal findings of laboratory data	2
Type of MM	
IgG, κ	7
IgA, κ	1
non secretory	1
Type of TRL/TMDS （FAB)	
TRL	
M2	1
M3	1
M5	1
M6	1
TMDS	
RA	2
RAEB	1
CMMoL	2

No.;number, Med.:median, diag.;diagnosis, yrs.;years, TRL;therapy;related leukemia, TMDS;therapy related myelodysplastic syndrome, MM;multiple myeloma,FAB;Frenchi-American-British classification, RA;refractory anemia, RAEB;refractory anemia with excess of blasts, CMMoL;chronic myelomonocytic leukemia

ISBN: 978-1-61804-111-1

Table 2. Cytogenetic abnormarity

Case 1	46,XX,-5,-7,+2mar
Case 2	46,XY,add(5),(q31),del(12),-16,+mar1
Case3	46,XY,add(7)
Case4	not determined
Case5	56,XX,-5,add(7)(q22),+8,add(12)(p11)
Case6	45,XY,idem,-7
Case7	44,XY,der(13;14)(q10;q10), 45,XY,der(13;14)(q10;q10)
Case8	46,XX
Case9	46,XY,+1,der(1;?)(q1-;p10),ins(1:?)(q11;?)

Table 3. Cumulative dose of anti-cancer agent (mg/body)

	MEL	CPM	ADR	VCR	MCNU
Case1	2888	7200			
Case2	1728	43200			
Case3	1440	1200	420		
Case4	864	21600			
Case5	1608	9600	300	46	
Case6	432	14400	360	48	1080
Case7	528	10200	540	34	850
Case8	744	9600	240	26	
Case9	1440	21600	400	36	

MEL;melphalan, CPM;cyclophosphamide, ADR;adriamycin, VCR;vincristine, MCNU;cymerin

ISBN: 978-1-61804-111-1