Review Articles

Therapy-Related Myeloid Malignancies in Myeloma.

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Competing interests: The authors have declared that no competing interests exist.

Abstract. Therapy related myeloid malignancies are an increasingly recognized treatment complication in patients undergoing therapy for multiple myeloma. The main predisposing factors are the alkylating agents, topoisomerase II inhibitors and radiotherapy, but recently questions have been raised regarding the immunomodulatory agent lenalidomide. Little is known about the new antimyeloma agents in the context of therapy related myeloid malignancies. The duration of treatment and the time from diagnosis are the main contributing factors in alkylating induced myeloid malignancies which occur 5-10 years after treatment, chromosome 5 and 7 abnormalities being the characteristic finding. High dose therapy (HDT) does not seem to be a major contributing factor *per se* in multiple myeloma. In a number of large published series, all the factors related with therapy-induced myelodysplasia were defined prior to HDT. Topoisomerase II inhibitors induce mainly acute leukemias which invariably correlate with dysregulation of the MLL gene. Radiotherapy causes therapy related myelodysplasia if applied in bone marrow producing areas, especially if combined with chemotherapy. Therapy related myeloid malignancies generally herald a poor prognosis. Karyotypic abnormalities seem to be the main prognostic factor. In all cases the risk for therapy related myeloid malignancies drops sharply by 10 years after the treatment.

Introduction. The problem of therapy related myelodysplastic syndromes (t-MDS) and acute myeloid leukemia (t-AML) in the context of cytotoxic chemotherapy is perhaps as old as the cytotoxic chemotherapy itself[1] and it is part of the more general problem of the second malignancies after cytotoxic chemotherapy.[2] It is a well known fact that as the overall survival (OS) for a malignant disease increases due to the treatment done, so the late effects of this treatment become much more evident with the advent of time.[3]

Multiple Myeloma (MM) is the second most prevalent hematological malignancy in the Western World[4] the last 15 years. Since the beginning of the era of chemotherapeutical agents in the 70's where the rate of complete remission (CR) for MM was below 3%, with the incorporation of tandem autologous hematopoietic cell –supported high dose therapy (HDT)[5,6] and the

newer agents as thalidomide, lenalidomide and bortezomib, the rate of CR has increased to over 80% under the Total Therapy TT3 protocol,[7] making the MM median OS well over the past three year landmark. In fact 10-year survivals of over 30% have been observed.[7] It is thus a natural consequence that the problem of t-MDS and t-AML becomes significant, requiring more attention form a biological perspective and likely requires special therpuetic considerations.

Epidemiology. It is rather appropriate that if one considers and examines the epidemiological data of t-MDS in MM to firstly acknowledge the fact that MDS and MM can co-exist *de novo*. Both the morphological[8] and the cytogenetic[9] evidence of this fact have been well described , with the cytogenetic anomalies seen in ~4% of the total MM patient population and having a distinctly different prognosis from the rest of the MM subtypes.[9] In a series of 648 MM patients that were enrolled in two non-HDT British Medical Research Council trials,[10] the 5-year actuarial prevalence and the 8-year prevalence of t-MDS were 3% and 10% respectively (FAB morphological criteria were used for t-MDS and t-AML diagnosis). This series brought to the forefront, the issue of MM-therapy related myeloid neoplasms, a fact that was preciously well known in the context of other hematologic malignancies. The Arkansas group reported on the cytogenetically defined MDS of more than 3000 MM patients that underwent HDT[11] and reported a prevalence of cytogenetically defined MDS of 3%. Most of the cytogenetic abnormalities (68%) were transient and clinical t-MDS and t-AML developed in 26 patients. It is therefore evident that there is a discrepancy of the reported prevalence and incidence of t-MDS in the various big series of the MM patients. Given the available knowledge on the main causes of t-MDS, one has to evaluate the incidence of MDS in the context of the therapeutic regimen given.

Conventional Chemotherapy and t-MDS in MM. The causative relationship of alkylating therapy in MM and t-MDS has been acknowledged as early as in the 1970s.[13,14] The widespread use of alkylating agents in various hematological and non hematological malignancies has resulted in valuable knowledge of the characteristics of the alkylating induced t-MDS. It is occurring mainly as a late event of the chemotherapy with a characteristic latency of 5-10 years.[15] Patients will present with t-MDS and evidence of bone marrow failure with at least one cytopenias while a minority will present as t-AML or t-myeloproliferative / myelodysplastic syndrome.[16] This category is commonly associated with unbalanced loss of genetic material, often involving chromosomes 5 and/or 7,

although that is not universal.[16] The decades of therapeutic experience has also contributed the knowledge that it is the amount of time and cumulative dosing of these agents and not the intensity of the therapy that contributes to the development of t-MDS. This fact is well established in many malignancies[17] and is also evident in the MM population.[10] Also well established is the knowledge that all alkylating agents are not the same in their leukaemogenic potential. Melphalan and BCNU are considered more leukaemogenic than cyclophosphamide in general[18] and this fact has also been established also in MM patients treated with these drugs.[10] The combination of alkylating agents and radiotherapy increases the incidence of t-MDS.[16]

The second category of t-MDS related to the conventional chemotherapy is related to the topoisomerase II inhibitors, namely adriamycin, etoposide, chemotherapeutics that interact through DNA topoisomerase II. This category of chemotherapeutics has long been successfully used in the treatment of MM. The t-MDS/AML that they produce has a latency period of 1-5 years, usually does not present as a t-MDS but as an overt t-AML from the beginning and is often associated with balanced chromosomal translocation.[16,17] The amount of cumulative dosage is equivocal and in the setting of the therapy of other hematological malignancies several regimen-related factors, as the schedule and concurrent use of asparaginase and G-SCF, are important in determining the relative risk.[18,19] Especially etoposide has strictly been associated with translocations of the MLL gene on chromosome band 11q23. MLL is a critical transcription regulator and the fact that there are over 40 partner genes in reciprocal translocations found in MDS/AML, suggests that it holds a crucial role in the pathogenesis of t-MDS/AML and MDS/AML in general.

In practice however most MM patients have received polychemotherapy of the above substances/modalities either concurrently or subsequently. The boundaries of the chromosomal, clinical and laboratory characteristics of the resulting t-MDS/AML characteristics regarding the causal chemotherapeutic are not always sharp.[11]

t-MDS/AML and HDT in MM. HDT has become the standard of care in the management of younger patients with symptomatic or progressive MM.[20,21] Tandem autotransplantation has doubled survival in relationship to standard-dose therapy.[22] Sizable series have reported on the development of t-MDS/AML in the context of HDT for Hodgkin, non-Hodgkin lymphoma as well as MM.[11,23,24] There is a clear tendency for attribution of t-MDS/AML, at least in the Hodgkin and non-Hodgkin

lymphomas, in HDT. Since standard dose regimens precede autologous peripheral blood stem cell (PBSC) collection and HDT, it is unclear whether the t-MDS is associated with HDT or the preceding chemotherapy. Primary HDT after non stem cell damaging vincristine – adriamycin- dexamethasone (VAD) therapy resulted in an incidence of t-MDS at 0% at 4.7 years.[25] In the biggest HDT MM series reported till now[11] multivariate analysis showed that the t-MDS/AML development was correlated with age -15% in 10 years for the older patients (>65 years), poor (<2.5x 10^6/kg) PBSC collection, time interval between the preceding chemotherapy and HDT reflecting longer pre transplant chemotherapeutic exposure and low platelet recovery 3 months after the first transplantation (<150x10^9/kg). The type of the HDT regimen was not significant in terms of subsequent t-MDS/AML development. From the aforementioned it appears that HDT is likely a contributing factor in t-MDS/AML, along with a host of other important ones. The later is supported from the fact that studies in lymphoma patients that applied fluorescence in situ hybridization (FISH) analysis for the detection of MDS lesions in interphase cells, found that such abnormalities were already present in PBSCs prior to HDT and were similar or identical to those subsequently detected after HDT.[26] Thus the question of the main contributing factor remains still open and could very well be that the main contribution of HDT to t-MDS/AML in MM is improvement in overall survival and patient longevity.

Newer Therapies and t-MDS in MM. Very little is known about the contribution or not to t-MDS of the newer MM therapies. There were not differences in the incidence of t-MDS between the thalidomide and control arm in the Arkansas Total Therapy 2 trial.[11] The recent reports on the association of lenalidomide with myeloid malignancies have born mixed results. The IFM 2005-02 study[27] and CALGB 100104 study[28] reported increased incidence of second primary malignancies, including myeloid malignanices, in the order of 5.5%-6.5%. In the MM-015 study, Palumbo et al[29] reported a 0.7% incidence of t-AML/t-MDS in MM transplant ineligible patients with use of lenalidomide combined with melphalan/prednisone and receiving additional lenalidomide maintenance, compared with those receiving melphalan/prednisone alone. This has given rise to the debate of optimal duration of maintenance with lenalidomide, as it clearly has shown progression free survival benefit in MM. To date, there have no reports regarding bortezomib in t-MDS/t-AML development in MM or lymphoma patients.

Therapeutic Modalities and Future Directions. It is

crucial for anyone to realize that preventing is far better than treating! Present and future efforts have to be -at least partially- directed towards the maximum effective anti-MM therapy with the lowest t-MDS potential. For conventional chemotherapy cumulative experience favors the short exposure to alkylating agents without intensity of treatment being a worrying factor in terms of t-MDS development. Radiotherapy perhaps should better be avoided upfront and concurrently with chemotherapy at least in bone marrow producing regions. There are enough data to support its leukaemogenic potential but not enough data to support its superiority in MM treatment at least compared with other therapeutic modalities. Bortezomib and thalidomide seem rather safe agents in MM regarding t-MDS.[30] The role of lenalidomide in t-MDS in the context of maintenance treatment in MM seems rather controversial. There is a clear need for more series with the maximum amount of uniformity for the rest of the MM treatment for someone to draw more definite conclusions.

Drug or xenobiotic metabolizing enzymes (DME) play central roles in the metabolism, biotransformation, and detoxification of xenobiotics and foreign compounds. They generally protect from potential harmful insults from the environment and also influence the metabolism of drugs (**Table 1**). Polymorphisms of these genes have been associated with the development of t-MDS/AML relative to the previous cytotoxic therapy. Although some of the reports are conflicting, the hall concept appears to be a very promising sector of pharmacogenomics and the individualization of cytotoxic therapy in general.[31]

The prognosis of t-MDS/AML is generally considered poor. An overall 5-year survival of less than 10% is commonly reported.[15] It is strongly associated with the underlying karyotypic abnormality, something that recently has been recognized in *de novo* MDS also, as it is portrayed in the revised IPSS that showed in the last International MDS Symposium (ISMDS 2011, Edinburgh May 18-21). Cases with abnormalities of chromosome 5 and/or 7 and a complex caryotype have a particular poor prognosis with a median survival of less than one year regardless of the number of myeloblasts present in bone marrow biopsy at initial MDS diagnosis.[32,33] Perhaps for these patients, an allogeneic transplantation should be strongly considered upfront. For not eligible patients autologous transplantation with PBSC collected early in the course of the patient could serve as an alternative. In the cases of 5q- chromosomal abnormalities lenalidomide has proved a valuable drug in releaving the accompanying anemia and in some cases inducing cytogenetic remission.[34] The drug can be given also to non 5q-MDS with a amount of myeloblasts <10% with good

Table 1. Role of gene polymorphism in t-MDS/t-AML development

Class		Glutathine-S Transferase pathway(GST)	Cytochorome P 450 system (CYP)	DNA Repair system
Alkylating Agents	Busulfan BCNU Cyclophosphamide Mechlorethamine Melphalan	GSTM1 GSTP1 GSTT1	CYP2B6 CYP2C19 CYP3A4	MGMT1 BER RAD51 XRCC3
Topoisomerase I Inhibitors	Irinotecan Topotecan		CYP3A	NHEJ (Non-homologous end joining)
Topoisomerase II Inhibitors	Daunorubicin Doxorubicin Etoposide Mitoxantrone Teniposide	GSTP1	CYP1B1 CYP3A4	NHEJ (Non-homologous end joining) RD51 XRCC3 NQ01
Ionizing Radiation				RD51 XRCC3 NQ01

results as long as the Gene Expression Profile of the MDS resembles the one of 5q- syndrome.[34] Hypo ethylating agents azacytidine and decitabine although have promising results in *de novo* high IPSS MDS, have not been tested enough in t-MDS/AML and the results in cases with 7 monosomy and complex caryotype are rather disappointing. Perhaps their use is better suited for cases of t-MDS with a number of myeloblasts>10% and karyotypic abnormalities that represent balanced translocations. This group can also benefit from the traditional chemotherapy approach at least for induction and/or salvage chemotherapy in terms of RAEB II MDS or t-AML. Of notice is the fact that the rare antracycline related Acute Promyelocytic Leukemias herald the exact same prognosis with the *de novo* ones,[35] a fact that highlights the importance of the underlying karyotypic abnormality in the prognostic

and therapeutical evaluation of t-MDS. Supportive care (erythropoietin agents, transfusion policy, iron chelating therapy) is the same as with the *de novo* MDS.

Conclusions. t-MDS represents a real and emerging problem in MM treatment. As the median MM OS survival universally increases it will possibly establish further its presence in the MM course. Although the diagnostic, prognostic and therapeutic capabilities of t-MDS and MDS in general are continuously expanding, one has to remember that "to prevent is always better than curing'' meaning that a good amount of present and future efforts has to be concentrated in the recognition and improvement of the MM therapy with the best anti myeloma effect and the fewer t-MDS complications.

References:

1. Rowley J, Golomb H, Vardiman J. Nonrandom chromosome abnormalities in acute leukemia and dysmyelopoietic syndromes in patients with previously treated malignant disease. Blood 1981; 58:759-767. PMid:7272506
2. Obedian E, Fischer DB, Haffty BG. Second Malignancies After Treatment of Early-Stage Breast Cancer: Lumpectomy and Radiation Therapy Versus Mastectomy JCO 2000;18:2406-2412
3. Doria R, Holford T, Farber LR, et al. Second solid malignancies after combined modality therapy for Hodgkin's disease. JCO 1995;13;2016-2022
4. Ries LAG, Melbert D, Krapcho M et al. SEER Cancer Statistics Review, 1973-1999, Bethesda, MD: National Cancer Institute, 2002.
5. Barlogie B, Jagannath S, Vesole D, et al. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. Blood. 1997;89:789-793. PMid:9028309
6. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003; 349:2495-2502. http://dx.doi.org/10.1056/NEJMoa032290 PMid:14695409
7. Barlogie B, Tricot G, van Rhee F, et al. Long-term outcome results of the first tandem autotransplant trial for multiple myeloma. Br J Haematol. 2006; 135:1365-2141. http://dx.doi.org/10.1111/j.1365-2141.2006.06271.x PMid:16939489
8. Mufti GJ, Hamblin TJ, Clein GP, et al. Coexistent myelodysplasia and plasma cell neoplasia. Br J Haematol. 1983;54:91 http://dx.doi.org/10.1111/j.1365-2141.1983.tb02070.x PMid:6849839
9. Jacobson J, Barlogie B, Shaughnessy JD, et al. MDS-type abnormalities within myeloma signature karyotype (MM-MDS): only 13% 1-year survival despite tandem transplants. Br J Haematol 2003;122:430–440 http://dx.doi.org/10.1046/j.1365-2141.2003.04455.x PMid:12877670

10. Cuzickl J, Erskine S, Edelman D et al. A comparison of the incidence of the myelodysplastic syndrome and acute myeloid leukaemia following melphalan and cyclophosphamide treatment for myelomatosis A report to the Medical Research Council's working party on leukaemia in adults. Br J Cancer 1987;55:523-529 PMid:3300761 PMCid:2001731

11. Barlogie B, Tricot G, Haessler J, et al. Cytogenetically defined myelodysplasia after melphalan-based autotransplantation for multiple myeloma linked to poor hematopoietic stem-cell mobilization: the Arkansas experience in more than 3000 patients treated since 1989. Blood 2008;111: 94-100 http://dx.doi.org/10.1182/blood-2007-06-097444 PMid:17895401 PMCid:2200826

12. Kantarjian HM, Keating MJ, Walters RS et al. Therapy-related leukemia and myelodysplastic syndrome: clinical, cytogenetic, and prognostic features. J Clin Oncol 1986;4:1748-1757 PMid:3783201

13. Kyle RA, Pierre RV, Bayrd ED. Multiple myeloma and acute myelomonocytic leukaemia. N Engl J Med 1970;283:1121-5. http://dx.doi.org/10.1056/NEJM197011192832101 PMid:5273282

14. Karchmer R, Amare M, Larsen W et al. Alkylating agents as leukemogenesis in multiple myeloma. Cancer 1974;33: 1103-1107 http://dx.doi.org/10.1002/1097-0142(197404)33:4<1103::AID-CNCR2820330432>3.0.CO;2-S

15. Pedersen-Bjergaard J, Andersen MK, Christiansen DH, et al. Genetic pathways in therapy-related myelodysplasia and acute myeloid leukemia. Blood 2002;99:1909-12 http://dx.doi.org/10.1182/blood.V99.6.1909 PMid:11877259

16. Larson RA. Therapy related myeloid neoplasms in WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues. Haematologica 2008;94:454-459 http://dx.doi.org/10.3324/haematol.2008.005157 PMid:19336749 PMCid:2663607

17. 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;102:43-52. http://dx.doi.org/10.1182/blood-2002-11-3343 PMid:12623843

18. Josting A, Wiedenmann S, Franklin J, t al. Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: a report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol 2003; 21:3440-6. http://dx.doi.org/10.1200/JCO.2003.07.160 PMid:12668650

19. Armitage JO, Carbone PP, Connors JM,et al. Treatment-Related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. J Clin Oncol 2003; 21:897-906 http://dx.doi.org/10.1200/JCO.2003.07.113 PMid:12610191

20. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma: Intergroupe Francais du Myelome. N Engl J Med. 1996;335:91-97. http://dx.doi.org/10.1056/NEJM199607113350204 PMid:8649495

21. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003; 348:1857-1883 http://dx.doi.org/10.1056/NEJMoa022340 PMid:12736280

22. Desikan R, Barlogie B, Sawyer J, et al. Results of high-dose therapy for 1000 patients with multiple myeloma: durable complete remissions and superior survival in the absence of chromosome13 abnormalities. Blood. 2000;95:4008-4010 PMid:10845942

23. van Leeuwen FE, Chorus AMJ, van den Belt- Dusebout AW, et al. Leukemia risk following Hodgkin's disease: relation to cumulative dose of alkylating agents, treatment with teniposide combinations, number of episodes of chemotherapy and bone marrow damage. J Clin Oncol. 1994; 12:1063-1073. PMid:8164031

24. Armitage J, Carbone P, Connors J, et al. Treatment- related myelodysplasia and acute leukemiain non-Hodgkin's lymphoma patients. J Clin Oncol. 2003;21:897-906. http://dx.doi.org/10.1200/JCO.2003.07.113 PMid:12610191

25. Govindarajan R, Jagannath S, Flick JT, et al. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. Br J Haematol. 1996;95:349-353. http://dx.doi.org/10.1046/j.1365-2141.1996.d01-1891.x PMid:8904891

26. Abruzzese E, Radford JE, Miller JS, et al. Detection of abnormal pretransplant clones in progenitor cells of patients who developed myelodysplasia after autologous transplantation. Blood. 1999; 94:1814-1819. PMid:10477708

27. Attal M, Lauwers VC, AMrit G, et al. Maintenance Treatment with Lenalidomide After Transplantation for MYELOMA : Final Analysis of the IFM 2005-02. Blood 2010;116:310

28. McCarthy PL, Owzar K, Anderson KC, et al. Phase III Intergroup Study of Lenalidomide Versus Placebo Maintenance Therapy Following Single Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Multiple Myeloma: CALGB 100104. Blood 2010;116: 37

29. Palumbo A, Delforge M, Catalano J, et al. Incidence of second primary malignancy (SPM) in melphalan-prednisone-lenalidomide combination followed by lenalidomide maintenance (MPR-R) in newly diagnosed multiple myeloma patients (pts) age 65 or older. J Clin Oncol 2011;29:8007

30. Ladetto M, Pagliano G, Ferrero S, et al. Major Tumor Shrinking and Persistent Molecular Remissions After Consolidation With Bortezomib, Thalidomide, and Dexamethasone in Patients With Autografted Myeloma. J Clin Oncol 2010; 28:2077-2084 http://dx.doi.org/10.1200/JCO.2009.23.7172 PMid:20308672

31. Leone G, Pagano L, Ben-Yehuda D, et al. Therapy-related leukemia and myelodysplasia: susceptibility and incidence. Haematologica 2007; 92:1389-1398. http://dx.doi.org/10.3324/haematol.11034 PMid:17768113

32. Singh ZN, Huo D, Anastasi J, et al. Therapy-related myelodysplastic syndrome: morphologic sub-classification may not be clinically relevant. Am J Clin Pathol 2007;127:197-205 http://dx.doi.org/10.1309/NQ3PMV4U8YV39JWJ PMid:17210514

33. Michiels JJ, McKenna RW, Arthur DC, et al. Therapy-related acute myeloid leukemia and myelodysplastic syndrome: a clinical and morphological study of 65 cases. Blood 1985;65:1364-1372 PMid:3857944

34. Ebert BL, Galili N, Tamayo P, et al. An erythroid differentiation signature predicts response to lenalidomide in myelodysplastic syndrome. PLoS Med 2008; 5:e35 http://dx.doi.org/10.1371/journal.pmed.0050035 PMid:18271621 PMCid:2235894

35. Beaumont M, Sanz M, Carli PM, et al. Therapy-Related Acute Promyelocytic Leukemia. J Clin Oncol 2003;21:2123-2137 http://dx.doi.org/10.1200/JCO.2003.09.072 PMid:12775738