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Therapy-related myelodysplasia and acute myeloid leukemia

Smita Bhatia, MD, MPH [Professor and Chair]
Department of Population Sciences Ruth Ziegler Chair in Population Research City of Hope Comprehensive Cancer Center Duarte, CA

Abstract

Therapy-related leukemia (t-MDS/AML) is a well known complication of conventional chemoradiotherapy used to treat a variety of primary malignancies including Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL), sarcoma, and ovarian and testicular cancer. The median time to development of t-MDS/AML is 3 to 5 years, with the risk decreasing markedly after the first decade. t-MDS/AML is the major cause of non-relapse mortality after autologous hematopoietic cell transplantation (HCT) for HL or NHL. The magnitude of risk of t-MDS/AML is higher, and the latency is shorter after HCT, compared to conventional therapy. Two types of t-MDS/AML are recognized depending on the causative therapeutic exposure: an alkylating agent/radiation-related type and a topoisomerase II inhibitor-related type. Interindividual variability in the risk for development of t-MDS/AML suggests a role for genetic variation in susceptibility to genotoxic exposures. Treatment of t-MDS/AML with conventional therapy is associated with a uniformly poor prognosis, with a median survival of 6 months. Because of the poor response to conventional chemotherapy, allogeneic HCT is recommended. Current research is focused on developing risk prediction and risk reduction strategies.

Epidemiology

Therapy-related leukemia (myelodysplasia and acute myeloid leukemia – t-MDS/AML) is a well known complication of conventional chemoradiotherapy for Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL),[1-3] acute lymphoblastic leukemia (ALL), sarcoma, and ovarian and testicular cancer.[4-9] The incidence of t-MDS/AML following conventional therapy ranges from 0.8% to 6.3% at 20 years. The median time to development of t-MDS/AML is 3 to 5 years, with the risk decreasing markedly after the first decade. t-MDS/AML is the major cause of non-relapse mortality after autologous hematopoietic cell transplantation (HCT)[10-19] for HL or NHL. The incidence of t-MDS/AML ranges from 1.1% to 24.3% at 5 years after autologous HCT. The median time to development of t-MDS/AML is 12 to 24 months after HCT. The magnitude of risk of t-MDS/AML is higher, and the latency is shorter after HCT, compared to conventional therapy.

Factors associated with an increased risk of t-MDS/AML include exposure to alkylating agents, topoisomerase II inhibitors, and radiation therapy,[12,19-23] and older age at treatment.[10,16] Among autologous HCT recipients, method of stem cell mobilization (use of

Smita Bhatia, MD, MPH, City of Hope National Medical Center, 1500 E. Duarte Road (MOB-4), Duarte CA 91010; Phone (626) 301-8426, Fax (626) 301-8978, sbhatia@coh.org.

peripheral blood stem cells and priming with etoposide for stem cell mobilization)[10,12] and transplantation conditioning with TBI[22] are associated with an increased risk of t-MDS/AML.

Two types of t-MDS/AML are recognized in the World Health Organization classification depending on the causative therapeutic exposure: an alkylating agent/radiation-related type and a topoisomerase II inhibitor-related type.[24] Alkylating agent-related t-MDS/AML usually appears 4 to 7 years after exposure to the mutagenic agent. Approximately two-thirds of patients present with MDS and the remainder with AML with myelodysplastic features.[25,26] Patients frequently present with cytopenias. Multilineage dysplasia is often present. There is a high incidence of abnormalities involving chromosomes 5 (−5/del(5q)) and 7 (−7/del(7q)). In contrast to alkylating agent-related t-MDS/AML, AML secondary to topoisomerase II inhibitors often does not have a preceding myelodysplastic phase, and presents as overt acute leukemia, often with a prominent monocytic component.[27,28] The latency period between the initiation of treatment with topoisomerase II inhibitors and the onset of leukemia is brief, with a median of 2 to 3 years.[28] Typically, the t-AML arising in such situations is associated with balanced translocations involving chromosome bands 11q23 or 21q22.[28]

Genetic susceptibility

Literature clearly supports the role of chemotherapy and radiation in the development of t-MDS/AML[29] but interindividual variability suggests a role for genetic variation in susceptibility to these genotoxic exposures. The risk of t-MDS/AML could potentially be modified by mutations in high-penetrance genes that lead to serious genetic diseases e.g., Li-Fraumeni syndrome,[30] and Fanconi anemia.[31-34] However, the attributable risk is expected to be very small because of their extremely low prevalence. The interindividual variability in risk of t-MDS/AML is more likely related to common polymorphisms in low-penetrance genes that are responsible for drug metabolism, transport and DNA repair. Genetic variation contributes 20% to 95% of the variability in cytotoxic drug disposition.[35] Polymorphisms in genes involved in drug metabolism and transport are relevant in determining disease-free survival and drug toxicity.[36] Variation in DNA repair plays a role in susceptibility to *de novo* cancer,[37-41] and likely modifies t-MDS/AML risk after exposure to DNA-damaging agents, such as radiation. Interaction of therapeutic exposures with underlying genetic characteristics that alter drug metabolism, transport or DNA repair may be associated with an increased risk of t-MDS/AML.

Drug Metabolism

Metabolism of genotoxic agents occurs in two phases. Phase I involves activation of substrates into highly reactive electrophilic intermediates that can damage DNA – a reaction principally performed by the cytochrome p450 (CYP) family of enzymes. Phase II enzymes (conjugation) function to inactivate genotoxic substrates. The phase II proteins comprise the glutathione S-transferase (GST), and NAD(P)H:quinone oxidoreductase-1 (NQO1). The balance between the two sets of enzymes is critical to the cellular response to xenobiotics; e.g., high activity of phase I enzyme and low activity of a phase II enzyme can result in DNA damage from the excess of harmful substrates. The xenobiotic substrates of CYP proteins include cyclophosphamide, ifosfamide, thiotepa, doxorubicin, and dacarbazine.[42] The CYPs transfer singlet oxygen onto their substrates creating highly reactive intermediates which, unless detoxified by phase II enzymes, have a strong ability to damage DNA.[43] The expression of these enzymes is highly variable among individuals because of several functionally relevant genetic polymorphisms. GSTs detoxify reactive electrophiles via conjugation to reduced glutathione, preventing damage to DNA. Polymorphisms exist in cytosolic subfamilies: μ [M], π [P), θ [T], and others. GSTs detoxify doxorubicin, lomustine,

busulfan, chlorambucil, cisplatin, cyclophosphamide, melphalan, etc.[44] Quinone oxidoreductase NQO1 uses the cofactors NADH and NADPH to catalyze the electron reduction of its substrates, produces less reactive hydroquinones, and therefore prevents generation of reactive oxygen species and free radicals which may subsequently lead to oxidative damage of cellular components. Individuals with at least one *GSTP1* codon 105 Val allele were shown to be significantly over-represented in t-MDS/AML cases compared with *de novo* AML cases (OR=1.8, 95%CI, 1.1-2.9). Also, relative to *de novo* AML, the *GSTP1* codon 105 allele occurred more often among t-MDS/AML patients with prior exposure to chemotherapy (OR=2.7, 95%CI, 1.4-5.1), particularly among those with prior exposure to known GSTP1 substrates (OR=4.3, 95%CI, 1.4-13.2) and not among t-MDS/AML patients with exposure to radiation alone.[45] An *NQO1* polymorphism has been shown to be significantly associated with the risk of t-MDS/AML.[46] In addition, individuals with the *CYP3A4-W* genotype may be at increased risk of t-MDS/AML, by increasing the production of reactive intermediates that might damage DNA.[47] A polymorphism profile consisting of *CYP1A1*2A*, del(*GSTT1*), and *NQO1*2* has been shown to modify the risk of t-AML/MDS. Absence of all three polymorphisms decreased the risk of t-AML/MDS; on the other hand, enhanced risk of t-AML/MDS was seen in the presence of only *NQO1*2* or all three polymorphisms.[48]

Drug transport

P-glycoprotein (encoded by MDR1) traps hydrophobic drugs in the plasma membrane of cells and effluxes them using an ATP-dependent process; many chemotherapeutic drugs are substrates of this protein. A number of polymorphisms exist in the *MDR1* gene, some proposed to be functional and evaluated as risk factors for t-MDS/AML.[49]

DNA repair

DNA repair mechanisms protect somatic cells from mutations in tumor suppressor genes and oncogenes that can lead to cancer initiation and progression. An individual's DNA repair capacity appears to be genetically determined.[50] A number of DNA repair genes contain polymorphic variants, resulting in large inter-individual variations in DNA repair capacity.[50] Even subtle differences in an individual's DNA repair capacity may be important in the presence of high-intensity genotoxic insults, such as chemotherapy or radiotherapy. Individuals with altered DNA repair mechanisms are likely susceptible to the development of genetic instability that drives the process of carcinogenesis. Over 80 DNA repair genes have been screened and demonstrate evidence of extensive polymorphic variation.[50]

The major repair pathways include mismatch repair, base excision repair, nucleotide excision repair, and DNA double-strand break repair and are described here, along with examples for studies addressing their involvement in the development of t-MDS/AML.

Mismatch repair (MMR) functions to correct mismatched DNA base pairs that arise as a result of misincorporation errors that have avoided polymerase proofreading during DNA replication.[51] Defects in the MMR pathway result in genetic instability or a mutator phenotype, manifested by an elevated rate of spontaneous mutations characterized as multiple replication errors in simple repetitive DNA sequences (microsatellites) – functionally identified as microsatellite instability (MSI). Approximately 50% of t-MDS/AML patients have MSI, associated with methylation of the MMR family member MLH1[52,53], low expression of MSH2[54], or polymorphisms in MSH2[55-58]. The appearance of MMR-deficient, drug-resistant clones during genotoxic treatment for a primary cancer could be a vital factor in t-MDS/AML susceptibility, particularly because the mutator phenotype would be expected to accelerate the accumulation of further mutations and

eventually SMN initiation. In addition, loss of MMR may result in deregulation of homologous recombination repair and consequent chromosomal instability.[59]

Double-Strand Breaks (DSBs) in DNA may lead to loss of genetic material, resulting in chromosomal aberrations. High levels of DSBs arise following ionizing radiation and chemotherapy exposures. Cellular pathways available to repair DSBs include homologous recombination (HR), non-homologous end-joining (NHEJ), and single-strand annealing.[60] HR uses the second, intact copy of the chromosome as a template to copy the information lost at the DSB site on the damaged chromosome – a high-fidelity process. RAD51 is one of the central proteins in the HR pathway, functioning to bind to DNA and promote ATP-dependent homologous pairing and strand transfer reactions.[61,62] *RAD51-G-135C* polymorphism is significantly over-represented in patients with t-MDS/AML compared with controls (C allele: OR=2.7).[63] XRCC3 also functions in the HR DSB repair pathway by directly interacting with, and stabilizing RAD51.[64] XRCC3, a paralog of RAD51, is also essential for genetic stability.[65,66] A polymorphism at codon 241 in the *XRCC3* gene results in a Thr➔Met amino acid substitution.[67] The variant *XRCC3-241Met* allele has been associated with a higher level of DNA adducts compared with cells with the wild type allele, implying aberrant repair[68] and has also been associated with increased levels of chromosome deletions in lymphocytes after exposure to radiation.[69] Although *XRCC3-Thr241Met* was not associated with t-MDS/AML (OR=1.4, 95%CI, 0.7-2.9), a synergistic effect resulting in an 8-fold increased risk of t-MDS/AML was observed in the presence of *XRCC3-241Met and RAD51-135C* allele in patients with t-MDS/AML compared with controls.[63] NHEJ pathway joins broken DNA ends containing very little homology. This process is not always precise and can result in small regions of non-template nucleotides around the site of the DNA break, potentially relevant in MLL-translocation associated with t-MDS/AML.

Base Excision Repair (BER) pathway corrects individually damaged bases occurring as a result of ionizing radiation and exogenous xenobiotic exposure. The XRCC1 protein plays a central role in the BER pathway and also in the repair of single strand breaks, by acting as a scaffold and recruiting other DNA repair proteins.[70,71] The protein also has a BRCA1 C-terminus (BRCT) domain – a characteristic of proteins involved in DNA damage recognition and response. The presence of variant *XRCC1-399Gln* has been shown to be protective for t-MDS/AML.[72]

Nucleotide Excision Repair (NER) removes structurally unrelated bulky damage induced by radiation and chemotherapy. The NER pathway is linked to transcription, and components of the pathway comprise the basal transcription factor IIH complex (TFIIH), which is required for transcription initiation by RNA polymerase II. One of the genes involved in the NER pathway (*ERCC2)* is a member of the TFIIH complex. The polymorphic Gln variant (*ERCC2 Lys751Gln*) is associated with t-MDS/AML.[73]

Pathogenesis

t-MDS/AML is a clonal hematologic disorder that is the consequence of an acquired somatic mutation induced by cytotoxic therapy in hematopoietic stem and progenitor cells, which confers a proliferative and/or survival advantage. t-MDS/AML after autologous HCT appears to result from genetic damage to the stem and/or progenitor cell from cytotoxic treatment, which may be potentiated by the transplant process itself through several mechanisms, including hematopoietic cell mobilization, collection, and storage, myeloablative chemotherapy and radiation, and the stress of engraftment and hematopoietic regeneration on the hematopoietic precursors.[13,74,75] Alkylating agents kill cancer cells by transferring alkyl groups to cellular molecules. Alkylation results in inaccurate base pairing

during replication and single- and double-strand breaks in the double helix as the alkylated bases are repaired.[76] Topoisomerase II inhibitors stabilize the enzyme–DNA covalent intermediate, decrease the re-ligation rate, and cause chromosomal breakage.[47,77] Repair of chromosomal damage results in chromosomal translocations, leading to leukemogenesis.[47,78,79] Most of the translocations disrupt a breakpoint cluster region between exons 5 and 11 of the band 11q23 and fuse mixed lineage leukemia (*MLL*) with a partner gene.[80-82] Translocations to 11q23 predominate following exposure to epipodophyllotoxins, whereas translocations to 21q22, inv(16), t(15,17), and t(9,22) most often occur following anthracyclines.[83]

The *p53* gene has a critical role in DNA damage response signaling, affecting cell cycle, cell death, and DNA repair pathways. Abnormal *p53* activity could lead to reduced ability to repair DNA damage, resulting in genomic instability and increased susceptibility to leukemogenesis. In patients with *de novo* MDS and AML, *p53* mutations are seen in fewer than 10% of patients. However, *p53* mutations have been identified in 27% to 50%[56,84,85] of the t-MDS/AML patients. These mutations are nongermline, restricted to the leukemic cells, and are more common after exposure to alkylating agents, with t-MDS/AML characterized by chromosome 5 and/or 7 losses. Ellis et al examined the association between t-MDS/AML and 2 common functional p53-pathway variants – the MDM2 SNP309 and the TP53 codon 72 polymorphism.[86] Neither polymorphism demonstrated a significant association. However, an interactive effect was detected such that MDM2 TT TP53 Arg/Arg double homozygotes, and individuals carrying both a MDM2 G allele and a TP53 Pro allele were at increased risk of chemotherapy-related t-MDS/AML. *TP53* modulates DNA repair and apoptosis upon DNA damage. A common germline polymorphism of *TP53*, P72R, produces a Proline to Arginine change that enhances apoptotic activity 15-fold. Ding et al demonstrated a significant interaction between P72R and C677T, a coding SNP in *MTHFR*. The homozygous T allele of C677T conferred and increased risk ($p < 0.001$) when combined with the Pro carrier of P72R (conferring decreased apoptotic activity) compared to its combination with homozygous Arg.[87]

Telomeres are noncoding regions of DNA that provide a cap at the ends of chromosomes and prevent dicentric fusion and other chromosomal aberrations.[88] Each somatic cell division is associated with a loss of telomere length. Cumulative telomere shortening can impose a limit on cell divisions and lead to cell senescence. Telomere shortening is also associated with genetic instability.[89] In hematopoietic tissues, there is progressive shortening of telomere length through life, with considerable variability between age-matched individuals.[90] Following genotoxic exposure, the increased replicative demand on hematopoietic cells associated with hematopoietic regeneration can lead to accelerated telomere shortening. Telomere shortening could contribute to development of t-MDS/AML by limiting hematopoietic proliferation and regenerative capacity and inducing genetic instability. Telomere length in serial peripheral blood samples from patients with t-MDS/AML after autologous HCT for lymphoma and matched lymphoma controls showed a sharp decline after day 100, but prior to development of t-MDS/AML.[91] In contrast, controls showed no significant changes in telomere length after day 100. These findings suggest that t-MDS/AML development is likely preceded by altered telomere dynamics in hematopoietic cells. Accelerated telomere loss in patients developing t-MDS/AML could reflect increased clonal proliferation and/or altered telomere regulation in pre-malignant cells.

Outcome

Treatment of t-MDS/AML with conventional therapy is associated with a uniformly poor prognosis, with a median survival of 6 months. Because of the poor response to conventional chemotherapy, allogeneic HCT has been attempted.[92-101] The BU/CY

conditioning regimen is associated with the best 5-year relapse free survival (43%) and lowest nonrelapse mortality (28%). Relapse rates are lower with unrelated donor transplants. Relapse probability and relapse-free survival correlate significantly with disease stage and karyotype. An optimized cytogenetic classification (adverse cytogenetics: abnormal 7 or complex; favorable cytogenetics: 5q– or 20q– or Y– or normal; intermediate: all others) is the strongest prognostic factor for overall survival through its impact on the risk of relapse.[99] After accounting for cytogenetics, patients with t-MDS/AML have an equivalent outcome to those with *de* novo disease.[100] A prediction model of survival after allogeneic HCT for t-MDS/AML has used the following 4 risk factors: i) age older than 35 years; ii) poor-risk cytogenetics; iii) t-AML not in remission or advanced t-MDS; iv) donor other than an HLA-identical sibling or a partially or well-matched unrelated donor. Five-year survival for subjects with none, 1, 2, 3, or 4 of these risk factors was 50%, 26%, 21%, 10%, and 4%, respectively.[102]

Risk Prediction and Risk Reduction Strategies

Because of the poor prognosis associated with t-MDS/AML, identification of early biomarkers would allow the timely use of appropriate measures to treat the disorder, such as reduced intensity conditioning (RIC), rather than waiting for the t-MDS/AML to present in the clinically overt form, when the disease burden would require higher-intensity therapy, with a greater risk of resultant morbidity. Several studies have attempted to correlate identification of genetically abnormal clones with subsequent risk of t-MDS/AML. Abnormal clones are frequently detected on cytogenetic analysis after autologous HCT for lymphoma and 30% to 50% of these patients develop overt t-MDS/AML.[13,14,21] Evaluation by FISH enhances sensitivity of detection of chromosomal abnormalities; significant levels of clonally abnormal cells were detected by FISH prior to high-dose therapy in 20 of 20 patients who developed t-MDS/AML, but only in 3 of 24 patients who did not.[103] Clonal hematopoiesis at the time of transplant using an X-inactivation-based clonality assay at the human androgen receptor locus (HUMARA), was predictive of the development of t-MDS/t-AML.[15] This assay is limited by its low sensitivity, requiring a high proportion of monoclonal cells to be present prior to reaching the threshold for detection, and is applicable only to female patients. Gene expression profile of ALL cells at diagnosis was shown to be predictive of risk of t-MDS/AML.[104] Altered gene expression (of genes regulating mitochondrial function, metabolism, and hematopoietic regulation) was observed in CD34+ cells from the peripheral blood stem cells (PBSCs) of patients who subsequently developed t-MDS/AML after autologous HCT for lymphoma when compared with controls who did not.[105] An optimal 38-gene PBSC classifier accurately distinguished patients who did or did not develop t-MDS/AML in an independent group of patients. The development of t-MDS/AML appears to require the acquisition of more than one mutation. Moreover, t-MDS/AML is a heterogeneous disorder with multiple subtypes characterized by different genetic abnormalities. Therefore, the identification of a single genetic abnormality may not necessarily have predictive value for development of t-MDS/AML.

It is possible to consider potential strategies to reduce the risk of t-MDS/AML, based on our understanding of the risk factors and pathogenesis of t-MDS/AML. Such strategies may include alteration in autologous stem cell procurement regimens to eliminate factors associated with increased risk of this complication. Standardized screening of patients in the immediate pre-HCT period with marrow pathology and cytogenetics could potentially help identify high risk populations that would then benefit from an allogeneic rather than autologous HCT. If strategies to develop predictors for patients at high risk prior to HCT are realized, alternative treatment approaches such as allogeneic transplantation or non-transplant modalities may be worth considering for patients identified being at increased risk of this complication.

Future Directions

Studies examining single gene polymorphisms in small heterogeneous samples can result in inconclusive results. Presence of functional redundancy results in a variant in one gene to have minimal consequences, whereas the combination of variants in two or more genes to potentially have more serious consequences resulting in the emergence of a malignant phenotype. Furthermore, there exists a need to systematically examine gene-therapy interactions, because of the absence of detailed therapeutic exposure data collected by the previous studies and the small sample sizes. A systematic assessment of the role of drug-metabolizing enzymes, DNA repair genes and drug transport in the development of t-MDS/AML is currently under way in a Children's Oncology Group-wide study, funded by the National Cancer Institute.

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Table 1

Magnitude of Risk and Populations at Increased Risk of Therapy-related Leukemia

Study	Study design	Sample size/ number of SMNs	Primary Diagnoses Type of HCT	Magnitude of Risk and Risk Factors
t-MDS/AML after autologous Hematopoeitic cell Transplantation				
Krishnan A et al. Blood. 2000;95:1588-1593[106]	Retrospective cohort study Nested case-control study	612/22 MDS/AML	Hodgkin lymphoma Non-Hodgkin lymphoma Autologous HCT	Cumulative probability of MDS/AM L : 8.6% at 6 years Stem cell priming with VP-16, pre-HCT radiation associated with increased risk of t-MDS/AML
Milligan DW et al. Br J Haematol. 1999;106:1020-1026[107]	Retrospective cohort design	4,998/ 66 MDS/AML	Hodgkin lymphoma Non-Hodgkin lymphoma Autologous HCT	5-year cumulative probability was 4.6% for HL and 3% for NHL. Older age at HCT, diagnosis of HL, exposure to TBI, multiple HCT, years between diagnosis were associated with increased risk of MDS/AML
Bhatia S, et al. Blood 1996;87:3633-9[10]	Retrospective cohort design	258/ 10 MDS/AML	Hematologic malignancies Autologous HCT	6-year cumulative probability was 13.5%. Peripheral blood stem cell transplantation Age >35 years at autologous hematopoietic cell transplantation
Friedberg JW, et al. J Clin Oncol 1999;17;3128-35[92]	Retrospective cohort design	552/41	Non-Hodgkin lymphoma	Fewer number of cells infused
t-MDS/AML after conventional therapy				
Koontz MZ et al. J Clin Oncol 2013;31:592-8[108]	Retrospective cohort design	754/24	Hodgkin lymphoma	10-year cumulative incidence ranged from 0.3% to 5.7%. Cumulative alkylating agent exposure increased the risk
Bhatia S et al. N Engl J Med 1996;334:745-51[3]	Retrospective Cohort design	1380/26	Hodgkin lymphoma	14-year cumulative probability was 2.8% Treatment with alkylating agents, age at diagnosis at 10 to 16 years (c/w <10 years), recurrence of primary disease risk, and a late stage of disease at diagnosis were associated with an increased
Bhatia S, et al. Blood 2002;99:4257-64[7]	Retrospective cohort design	8831/14	Acute lymphoblastic leukemia	15-years cumulative incidence was 0.3%; relapse of primary disease was associated with increased risk
Bhatia S et al. Blood 2007;109:46-51[6]	Retrospective cohort study design	578/11	Ewing sarcoma	5-year cumulative incidence of 2%; increasing exposure from 90 g/m2 to 140 g/m2; cyclophosphamide from 9.6 to 17.6 g/m2 and doxorubicin from 375 to 450 mg/m2 increased the risk
Travis LB et al. N Engl J Med. 1999;340:351-7[9]	Case-control study design	Cases: 96/ controls: 272	Ovarian cancer	Relative risk for treatment with carboplatin and cisplatin increased the risk in a dose-dependent fashion

Study	Study design	Sample size/ number of SMNs	Primary Diagnoses Type of HCT	Magnitude of Risk and Risk Factors
Travis LB et al. J Natl Cancer Inst 2000;92:1165-71[8]	Case-control study design	Cases: 36; controls: 106	Testicular cancer	Radiation to active bone marrow (dose-dependent relation); cumulative dose of cisplatin