Diplomarbeit

Inzidenz von Therapie-assoziiertem myelodysplastischen Syndrom und akuter myeloischer Leukämie nach konventioneller Therapie oder autologer Stammzelltransplantation bei Morbus Hodgkin: ein Systematischer Review

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Graz, im März 2009

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Zusammenfassung

Ziel der Studie: Therapie-assoziierte(s) myelodysplastisches Syndrom (t-MDS) und akute myeloische Leukämie (t-AML) stellen eine oftmals letale Spätkomplikation der Therapie von Patienten mit Morbus Hodgkin dar. Verlässliche Inzidenzangaben für die beiden Therapiemodalitäten - konventionelle Radio-Chemotherapie und Hochdosistherapie mit autologer Stammzelltransplantation (ASCT) - fehlen.

Methodik: Um diese Frage zu beantworten, führten wir einen systematischen Review durch. Über die Datenbanken MEDLINE, EMBASE und Cochrane Library sowie durch Screening von Konferenzbeiträgen und Referenzlisten wurden jene Originalarbeiten identifiziert, die definierten Suchbegriffen entsprachen. Diese wurden sodann auf Erfüllung von Einschlußkriterien geprüft. Die relevanten Daten wurden aus den ausgewählten Originalarbeiten extrahiert und analysiert.

Ergebnisse: Zwischen 1979 und 2008 wurden 3266 Originalarbeiten identifiziert, von denen 56 den Einschlußkriterien entsprachen. In 55 Kohortenstudien und einer randomisierten, kontrollierten Studie (RCT) wurde über 30572 Patienten berichtet. 49 Studien behandelten die konventionelle Therapie und 6 die Hochdosistherapie mit ASCT. Das mediane Follow-up lag zwischen 5 und 17.8 Jahren. Es wurden insgesamt 270 Fälle von t-MDS/t-AML beobachtet. Das am häufigsten verwendete Inzidenzmaß war die „crude incidence“ welche von 0 bis 5.4% im konventionellen und von 1,9% bis 14,8% im ASCT Setting reichte. Die eine randomisierte kontrollierte Studie, die konventionelle Therapie mit ASCT verglich, gab eine Inzidenz von t-MDS/t-AML von 0.9% bzw. 2% an.

Schlußfolgerung: Die Ergebnisse dieses systematischen Reviews weisen darauf hin, dass die Hochdosistherapie mit ASCT höhere Inzidenzen an t-MDS/t-AML als die konventionelle Therapie bei Patienten mit HD aufweist. Dies ist ein wesentlicher Indikator für die Rolle von kumulativer Toxizität in der Pathogenese dieser sekundären Neoplasien.

Abstract

Purpose: Therapy-related myelodysplastic syndrome (t-MDS) and acute myeloid leukaemia (t-AML) are serious long-term complications following cytotoxic treatment of patients with Hodgkin's disease (HD). However, reliable data on incidence of t-MDS/t-AML following conventional radio-chemotherapy or high-dose therapy with autologous stem cell transplantation (ASCT) are lacking.

Design: To answer this question, a systematic review was performed. We screened the databases MEDLINE, EMBASE and Cochrane Library as well as conference proceedings and reference lists using appropriate key words. Original articles identified were checked for fulfilling strict inclusion criteria. Relevant data were then extracted form selected articles and analysed.

Results: Of 3266 original articles, identified between 1979 und 2008, 56 fulfilled the inclusion criteria. Fifty-five cohort studies and one randomized controlled trial (RCT) reported on 30.572 patients. Forty-nine articles presented data on conventional and six on high-dose therapy with ASCT. The median follow-up was between five and 17.8 years. A total of 270 cases of t-MDS/t-AML were observed. "Crude incidence" was the most frequent measure showing a range from 0 to 5.4% in the conventional and 1.9 to 14.8% in the high-dose therapy/ASCT group. The only RCT that compared conventional and high-dose therapy with ASCT reported an incidence of t-MDS/t-AML of 0.9% and 2%, respectively.

Conclusion: The results of this systematic review demonstrate that high-dose therapy with ASCT is associated with higher incidences of t-MDS/t-AML as compared to conventional therapy in patients with HD. This indicates that toxicity plays a role in the pathogenesis of these secondary malignancies.

Diploma thesis

Incidence of therapy-related myelodysplastic syndrome/ acute myeloid leukaemia after conventional therapy or autologous stem cell transplantation for Hodgkin's disease: a systematic review

In order to attain the academic degree
"Doctor medicinae universae"

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1 INTRODUCTION

1.1 Long-term consequences of antineoplastic therapy

Antineoplastic therapies include chemo- and radiotherapy, haematopoietic stem cell transplantation, immuno- and targeted therapies as well as combined modality treatment approaches. These different strategies imply the possibility to cure patients from cancer. However, most of these therapies do not only affect malignant cells but also influence the function of healthy cells. Therefore, side effects and long-term complications are common.

Temporary side effects like hair loss, nausea, vomiting, diarrhoea, haemorrhagic cystitis and fatigue will subside shortly after discontinuation of the antineoplastic treatment. Most short-term side effects can be alleviated by medication. However, some treatment strategies induce late and long-term sequelae resulting in organ damage and functional impairment. Well known are radiotherapy induced skin lesions like hyperpigmentation, teleangiectases, atrophy and ulcerations of mucous membranes. Other antineoplastic drugs like carboplatin and cisplatin, cyclophosphamide and ifosfamide affect the kidney function and may lead to renal failure. One might also not underestimate the cardiotoxicity of certain chemotherapy drugs. Anthracyclins can induce arrhythmias, heart failure and infarction and are associated with hypo- as well as hypertension. The most common manifestation of pulmonary toxicity is chronic pneumonitis with progressive lung fibrosis. The liver with its central role in metabolism is at great risk of being damaged by antineoplastic agents. Liver cell damage can lead to by fibrosis and cirrhosis and even veno-occlusive disease. Gonadal dysfunction may be a reason for therapy-related infertility.

However, the most severe late treatment complication is a secondary malignancy (Lenz et al., 2004, Brusamolino et al., 1998). Due to better treatment strategies, which also includes progress in supportive care, more and more patients survive their primary neoplasm. This treatment success enables patients to become long-term survivors of a cancer that otherwise had an inevitably fatal outcome. The

three most common secondary neoplasms are therapy-related myelodysplastic syndrome (t-MDS) and acute myeloid laeukaemia (t-AML), non-Hodgkin's lymphomas and solid tumours (Kalaycio et al., 2006).

1.2 Myelodysplastic syndromes and acute myeloid leukaemia

1.2.1 Definition

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal haematological disorders resulting in ineffective haematopoiesis (Valent et al., 2007, Cheson, 1997).Qualitative and quantitative changes in haematopoiesis result in a dysplastic, hypercellular bone marrow with various degrees of malignant blast cells and peripheral cytopenias. The process of neoplastic transformation occurs at the level of the haematopoietic stem- and precursor cell. The MDS are characterised by a decreasing capacity of physiological self renewal and increasing restriction to the myeloid lineage. Although the MDS are previously termed "pre-leukaemia", they represent truly neoplastic disorders. Approximately one-third of patients with MDS progresses to acute myeloid leukaemia within months to a few years.

Acute myeloid leukaemia (AML) is a haematopoietic malignancy characterised by an increase of malignant blasts cells of the myeloid lineage of 20% or more according to the WHO classification (*Figure 1*). The neoplastic clone is either established at the level of the haematopoietic stem- and precursor cell or – more frequently - at the committed myeloid progenitor cell. This leukaemia is characterised by a rapid proliferation of blasts in the bone marrow/ peripheral blood and an arrest in their maturation. Massive production of neoplastic cells interferes with the production of normal blood cells resulting in haematopoietic insufficiency with neutropenia and/or anaemia and/or thrombocytopenia.

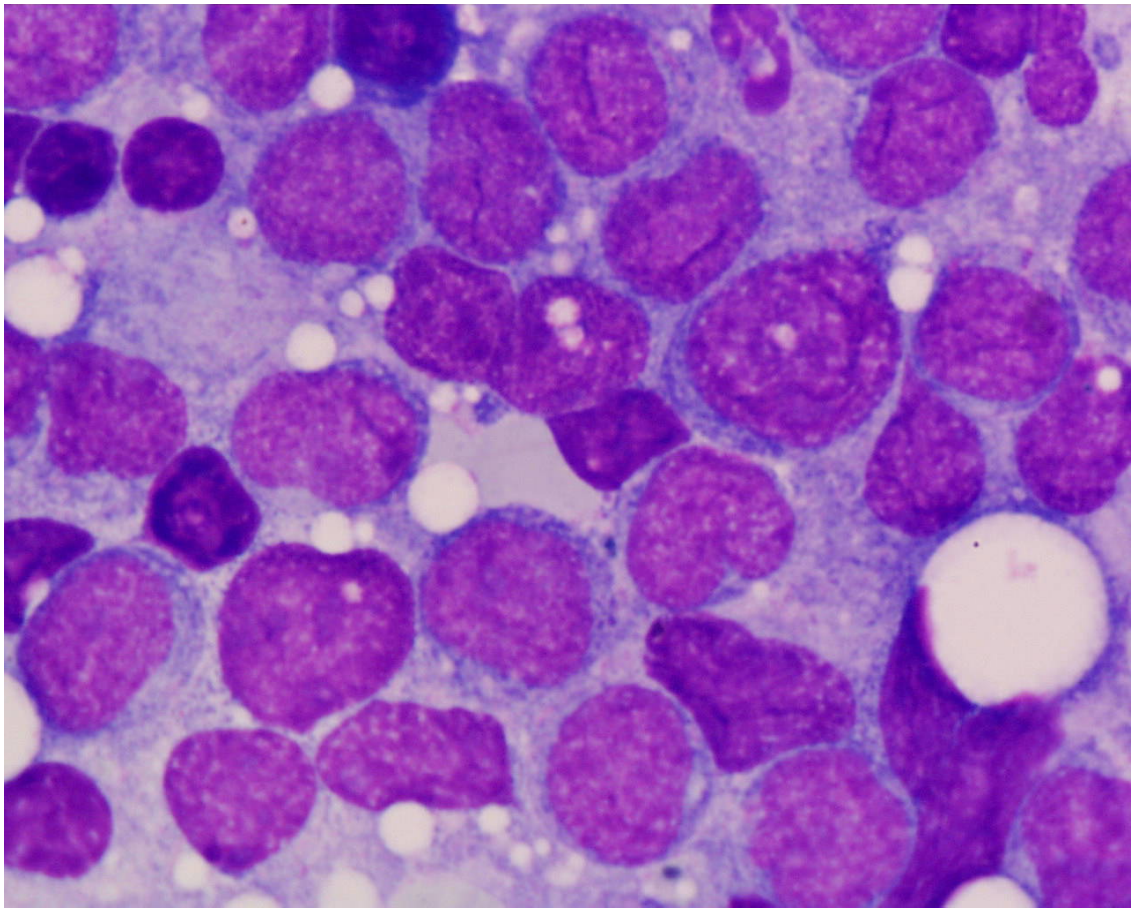


Figure 1. ***Bone marrow infiltration in acute myeloid leukaemia.*** *The blast cells are of medium to large size, have prominent nuclei sometimes featuring one nucleolus. The cytoplasm is basophilic without vacuoles, granules or Auer rods.*

1.2.2 Signs and Symptoms

The symptoms of MDS and AML are similar and caused by the replacement of normal bone marrow with malignant, dysplastic or leukaemic cells. The decrease in red and white blood cells as well as platelets results in bone marrow failure which constitutes a life-threatening condition. Signs and symptoms of MDS and AML are, however, diverse and non-specific often delaying a proper diagnosis. They represent the consequence of anaemia, neutropenia and/or thrombocytopenia. A lack of red blood cells causes fatigue, paleness, shortness of breath and ultimately, patients may become unconscious. Neutropenia leads to opportunistic infections including fungal infections and sepsis, which are still one of the leading causes of morbidity and mortality in patients with haematological malignancies. Ineffective thrombopoieses results in a low platelet count and clinically to petechiae, easy bruising and bleeding.

Patients with haematopoietic failure due to a malignant disease also present with weight loss, loss of appetite, bone and joint pain. Leukaemic infiltration of various tissues including the liver, spleen, skin, lymph nodes, gingiva and central nervous system can produce a variety of organ-specific symptoms. However, a few individuals are asymptomatic and diagnosis of MDS/AML is made incidentally on a routine medical check-up.

1.2.3 Diagnosis

The first clue to the diagnosis of MDS/AML is typically an abnormal result of a complete blood count featuring cytopenia in one or several cell lines (Young and Iland, 2007). This is followed by a thorough morphological examination of a peripheral blood and bone marrow smear stained with May-Grünwald Giemsa. Whereas the peripheral blood presents with cytopenia, the bone marrow exhibits most often increased cellularity. In MDS, this is a sign of ineffective haematopoiesis. There is often a predominance of immature myeloid cells. The granulocytic series shows dysplastic features with hypogranular cells and hypo-/ hypersegmented nuclei. In the megakaryocytic series, there are degranulated, ballooned platelets and hypo-/ hypersegmented nuclei of megakaryocytes as well as microkaryocytes. Other morphological abnormalities include megaloblastic red cell precursors with multiple nuclei and ringed sideroblasts representing erythroid precursors with iron-loaded mitochondria. Other causes of dysplasia like vitamin B12 or folate deficiencies, viral infections including HIV and renal failure have to be ruled out. Per definition, acute myeloid leukaemia can be diagnosed when more than 20% or more leukaemic blast cells are present in the bone marrow or peripheral blood (*Figure 1*).

Examination of blast cells by **cytochemistry** is a mandatory diagnostic tool. Staining for myeloperoxidase is performed to detect myeloblasts, monoblasts are positive using esterase stains and lymphoblasts may be positive for periodic acid Schiff stains (PAS). Morphologic examination of peripheral blood and bone marrow smears is still the basis of MDS and leukaemia diagnosis worldwide. However, its sensitivity in distinguishing acute myeloid from acute lymphoid leukaemia (ALL) is low

and approaches just 70%. Therefore, further investigations are necessary for unumbiguous therapeutic decisions.

Immunophenotyping of leukaemic blasts is the detection of cytoplasmic and cell surface antigens with appropriate monoclonal antibodies. This plays a crucial role in identifying the leukaemia origin, whether it is myeloid or lymphatoid in nature, in defining the maturation stage and detecting aberrant antigens. It is further a useful tool for individual treatment monitoring and detection of (minimal) residual disease. The sensitivity of immunophenotyping in distinguishing AML from ALL is 98%.

CD	Antibodies, Myeloid Lineage	M1,M2	M3	M4,M5	M6	M7
CD11b	Mo1, Leu15	+/-	+/-	++	-	-
CD13	MY7, Leu-M7	++	++	++	++	+
CD14	MY4, Mo2, Leu-M3	+/-	-	++	++	-
CD15	Leu-M1	++	++	++	++	-
CD33	MY9, Leu-M9	++	++	++	++	+
	Antibodies, stem cell					
CD34	MY10, HPCA-1	+	-	+/-	+	+
CD38	Leu-17	+	+	+	+	+

Table 1. Immunological markers (CD, cluster of differentiation) used for AML diagnosis

Genetic features. Leukaemic blasts exhibit characteristic, chromosomal aberrations in about 50% of cases. These aberrations are somatic in origin and therefore, restricted to neoplastic cells. Chromosomal aberrations are useful for both, diagnostic and prognostic purposes. They form an essential part of fundamental treatment decisions, e.g. whether a patient has to undergo allogeneic stem cell transplantation. The samples of interest are tested for chromosomal aberrations by conventional cytogenetic analysis and/or fluorescent in situ hybridization (FISH). The most common abnormalities are: translocation t(15;17), t(8;21) and inversion (16) indicating a good prognosis; 11q23 rearrangements and deletion of all or part of chromosomes 5 and or 7, indicating a poor prognosis (Leone et al., 1999).

1.2.4 Classification

Myelodysplastic syndromes are classified according to the World Health Organization (Vardiman et al., 2002) :

- **Refractory anaemia** (RA)
- **Refractory anaemia with ringed sideroblasts** (RARS)
- **Refractory cytopenia with multilineage dysplasia** (RCMD)
- **Refractory cytopenia with multilineage dysplasia and ringed sideroblasts** (RCMD-RS)
- **Refractory anaemia with excess blasts I and II**
- **5q- syndrome**
- **Myelodysplasia unclassifiable**

The category of refractory cytopenia with multilineage dysplasia includes patients with pathological changes seen in other myeloid lineages than red cells as well (i.e. dysplastic white cell precursors and megakaryocytic dysplasia). RAEB is divided into RAEB-I with 5-10% and RAEB-II with 11-19% blast cells, which has a poorer prognosis than RAEB-I. The 5q-syndrome is frequently encountered in older women. They present with leukopenia, normal or elevated platelet counts and mononuclear megakaryocytes in the bone marrow. Neoplastic cells typically harbour a deletion of the long arm of chromosome 5. The prognosis of patients with the 5q-syndrome is somewhat better than of other subtypes.

The International Prognostic Scoring System (IPSS) is a clinical tool to assess the prognosis of MDS patients (Valent et al., 2007). This system takes into account the number of cytopenias in the peripheral blood, the percentage of blast cells in the marrow and results of cytogenetic analysis. Patients with a low-risk score have a median survival of 5.7 years, high-risk individuals of only 3 months (*Table 2*).

Variable	Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	<5	5-10	-	11-20	21-30
Karyotype	Good	Intermediate	Poor	-	-
Cytopenias	0/1	2/3	-	-	-
Risk group	IPSS score				
Low	0				
Intermediate-1	0.5-1.0				
Intermediate-2	1.5-2.0				
High	2.5-3.5				

Table 2. The International Prognosis Scoring System (IPSS) for patients with MDS

The French, American, British (FAB) classification system divides AML into eight subtypes, M0 through to M7, based on the type of cell from which the leukaemia originated and its degree of maturation (Tallman, 2004). This is done by examining the appearance of the malignant cells under the microscope and by performing cytochemistry stains.
The eight FAB subtypes are:

- **M0** minimally differentiated acute myeloblastic leukaemia
- **M1** acute myeloblastic leukaemia, without maturation
- **M2** acute myeloblastic leukaemia, with granulocytic maturation
- **M3** promyelocytic, or acute promyelocytic leukaemia (APL)
- **M4** acute myelomonocytic leukaemia
- **M4eo** myelomonocytic leukaemia associated with bone marrow eosinophilia
- **M5** acute monoblastic leukaemia (M5a) or acute monocytic leukaemia (M5b)
- **M6** acute erythroid leukaemia, including erythroleukaemia (M6a) and very rare pure erythroblastic leukaemia (M6b)
- **M7** acute megakaryoblastic leukaemia

According to the WHO criteria, the diagnosis of AML is established when more than 20% leukaemic myeloblasts are present in the bone marrow and/or peripheral blood. The WHO classification attempts to become a clinically orientated tool with more reliable prognostic information than the FAB classification. This system not only incorporates morphology and cytochemistry, but also immunological and cytogenetic data.

The WHO subtypes of AML are (Vardiman et al., 2002) :

AML with characteristic genetic abnormalities. It includes AML with translocations between chromosome 8 and 21 [t (8;21)], inversions of chromosome 16 [inv(16)], or translocations between chromosome 15 and 17 [t (15;17)]. Patients with AML in this category generally have a high rate of remission and a better prognosis as compared to other types of AML.

AML with multilineage dysplasia. This category includes patients who have had a prior myelodysplastic syndrome or myeloproliferative disease that transformed to AML. This category of AML occurs most often in elderly patients and has a dismal prognosis.

AML and MDS, therapy-related. This category includes patients who have had prior chemotherapy and/or radiation for a primary disease and subsequently developed AML or MDS. These leukaemias are characterized by specific chromosomal abnormalities, and often carry a worse prognosis.

AML not otherwise categorized. Includes subtypes of AML that do not fall into the above categories.

Acute leukaemia of ambiguous lineage. Acute leukaemia of ambiguous lineage (also known as mixed phenotype or biphenotypic acute leukaemia) is diagnosed when leukaemia cells can not be classified as either myeloid or lymphoid cells, or where both types of cells are present.

1.3 Therapy-related myelodysplastic syndrome and acute myeloid leukaemia

1.3.1 Definition

Therapy-related myelodysplasia (t-MDS) and therapy-related acute myeloid leukaemia (t-AML) are increasingly recognized late treatment complications in patients treated with chemo- and/or radiotherapy for a primary haematological malignancy, a solid tumor or a non-malignant disease (Sobecks et al., 1999), (Josting et al., 2003). The term t-MDS/ t-AML is used to describe a clinical syndrome that includes important differences from MDS/AML that arise de novo (Thirman and Larson, 1996). The nomenclature “therapy-related” is a more precise one then the term “secondary MDS/AML” as it indicates a possible, causal relationship to previous cytotoxic therapies.

1.3.2 Biology

According to the WHO classification, t-MDS and t-AML are regarded as one entity due to the same aetiology and pathogenesis. Although the diagnosis of t-AML is a straightforward one, that of t-MDS is more difficult to establish. Not only cytopenia and dysplasia are compulsory but also an increase in blast cells and/ or clonal cytogenetic aberrations, the latter being observed in more than 90% of cases. Two different types of t-MDS/t-AML are observed: t-AML in patients treated with drugs inhibiting the enzyme DNA-topoisomerase II (e.g. etoposide, doxorubicin, daunorubicin, mitoxantrone) and in those treated with alkylating agents (e.g. melphalan, cyclophosphamide, nitrogen mustard) or radiation (Leone et al., 1999). Topoisomerase II inhibitors block the enzymatic reaction thereby leaving DNA with a permanent strand break. DNA-strand breaks which are not repaired properly usually lead to apoptosis. However, in the case of leukaemia initiation, these strand breaks persist thereby contributing to genomic instability and the development of a malignant clone. Leukaemia following topoisomerase II Inhibitors has a much shorter latency between the initial cytotoxic therapy and diagnosis of t-AML. A preceding myelodysplastic phase is rarely observed in these leukaemias. In contrast, alkylating agents and radiotherapy induce leukaemia four to six years after initial therapy. These

patients often present with a myelodysplastic syndrome that transforms to overt AML in more than 50% of cases. Alkylator-induced MDS/AML show chromosome 7 and/or 5 losses or partial deletions, while balanced translocations involving chromosome bands 11q23 and 21q22 are the result of DNA-topoisomerase II inhibitors (Thirman and Larson, 1996).

1.3.3 Therapy

Treatment of t-MDS/t-AML remains disappointing. The prognosis of these patients is generally poor with a median survival from diagnosis of t-MDS/t-AML of less than six months. Therapeutic options are supportive care including red blood cell and platelet transfusions, antibiotics, chemotherapy, haematopoietic growth factors like G-CSF or erythropoietin, and haematopoietic stem cell transplantation. Intensive chemotherapy is given to induce a remission. However, complete remission (CR) rates and remission duration are lower compared to de novo MDS/AML cases. The only possible curative therapy is allogeneic haematopoietic stem cell transplantation, which is feasible in a small proportion of t-MDS/t-AML cases only (Witherspoon et al., 2001),(Chang et al., 2007),(Yakoub-Agha et al., 2000). This approach is complicated by a high rate of treatment related mortality of up to 60% and low long-term survival rates of only 30% (Henry-Amar and Dietrich, 1993).

1.4 Hodgkin's disease

Hodgkin's disease (HD) is one of the most frequent primary haematological tumours with an incidence of 3/100000/year (Franklin et al., 2005). Hodgkin's disease, also called Hodgkin's lymphoma, is a malignancy that originates in the lymphatic system. Two age-related peaks are observed: one between 15-35 and another one between 60-70 years of age.

The cancer cells in HD are called Hodgkin- and Reed-Sternberg cells and are derived from B-lymphocytes (Brauninger et al., 2006, Kuppers, 2009). Hodgkin- and Reed-Sternberg cells reside in an infiltrate containing a variable mixture of non-

neoplastic small lymphocytes, plasma cells, fibroblasts and collagen fibres. The two main types of HD are classical HD with its 4 subtypes (nodular sclerosis, lymphocyte predominance, mixed cellularity and lymphocyte depleted) and nodular lymphocyte predominant HD (Kuppers, 2009). Nodular sclerosing classical Hodgkin's disease is the most common subtype and is composed of large tumor nodules with lacunar Reed Sternberg (RS) cells. The mixed-cellularity subtype is a common subtype consisting of classic RS cells admixed with numerous inflammatory cells including lymphocytes, histiocytes, eosinophils, and plasma cells.

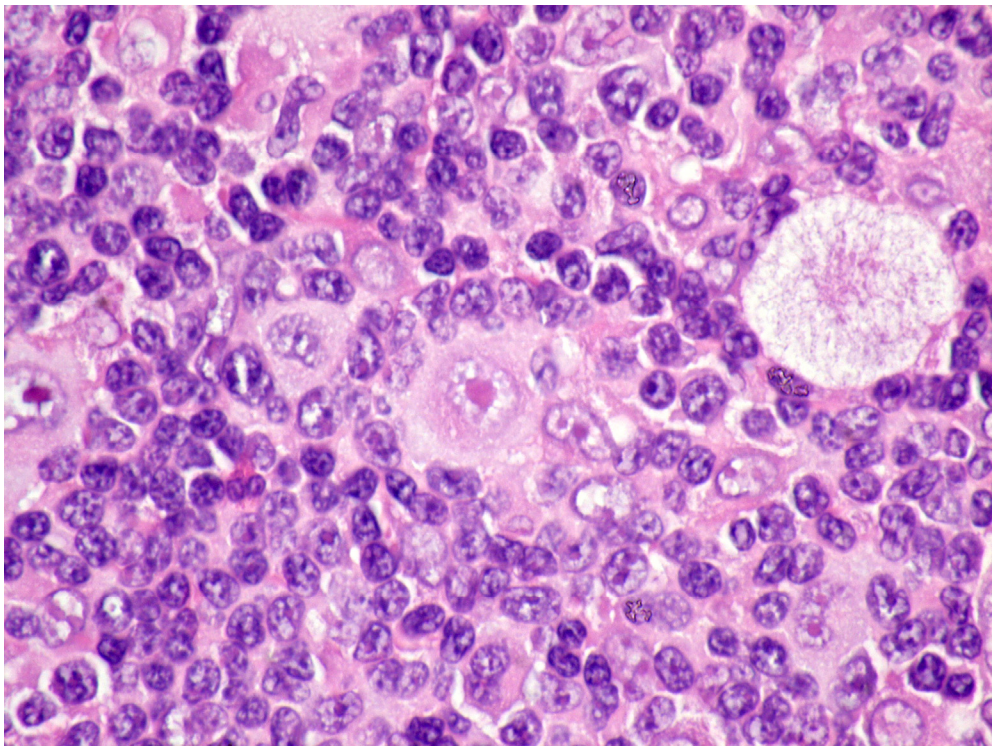


Figure 2a. Lymph node specimen of a patient with HD.

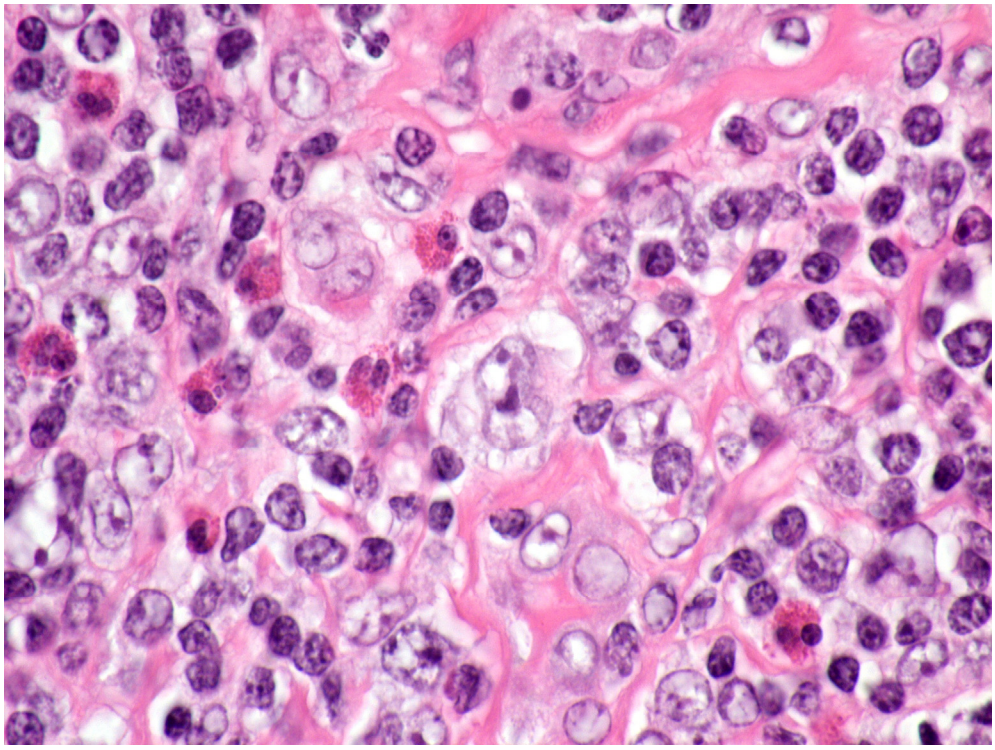


Figure 2b. ***Reed-Sternberg cells.*** *The RS cells are large cells that are either multinucleated or have a bilobed nucleus with prominent eosinophilic inclusion-like nucleoli.*

The first sign of HD is often an enlarged lymph node that appears without a concomitant infectious disease (Earl et al., 1980). However, as innate or acquired lymphatic tissue is present in almost any part of the human body, HD can originate almost everywhere. The disease spreads through lymphatic vessels to adjacent lymph nodes and may later infiltrate extralymphatic tissues and organs as the lungs, liver or bone marrow.

Patients with Hodgkin's disease may present with the following symptoms:

- Lymph nodes: the most common sign/symptom of HD is painless enlargement of one or more lymph nodes. The nodes may also feel rubbery and swollen. The cervical and supraclavicular regions are most frequently involved (80-90%). Lymph nodes of the chest or abdomen can be affected, too, and may form large conglomerate tumors (“bulky disease”).
- Splenomegaly: enlargement of the spleen occurs in about 30% of patients with Hodgkin's lymphoma. The enlargement, however, is rarely massive and the size of the spleen may fluctuate during treatment courses.

- Systemic symptoms: about one-third of patients with Hodgkin's disease may also present with systemic symptoms, including low-grade fever; night sweats; unexplained weight loss of at least 10% of the patient's total body mass in six months or less; pruritus due to increased levels of eosinophils in the bloodstream; or fatigue. Systemic symptoms such as fever, night sweats, and weight loss are known as B symptoms. Thus, the presence of fever, weight loss, and night sweats indicate that the patient's stage is, for example, 2B instead of 2A (Jose et al., 2005).

The diagnosis of HD is based on the recognition of Hodgkin- and/or Reed-Sternberg cells in an appropriate cellular background in tissue sections from a lymph node or extra-lymphatic organ, such as the bone marrow, lung or bone. Fine needle aspiration biopsy is not adequate for the diagnosis of HD as too little material for histologic and immunohistochemistry studies is obtained.

The staging system for HD is a clinical staging system established at the Ann Arbor conference with the addition of a definition of bulky disease (Fuchs et al., 2006):

- Stage I is involvement of a single lymph node region (I) or a single extralymphatic site (IE);
- Stage II is involvement of two or more lymph node regions and/or localized extralymphatic lesion on the same side of the diaphragm (II);
- Stage III is involvement of lymph node regions and/or localized extralymphatic lesion on both sides of the diaphragm, which may include the spleen (IIIE)
- Stage IV is diffuse or disseminated involvement of one or more extralymphatic organs or sites.

Bulky tumor is defined as a single mass of tumor tissue exceeding 10 cm in largest diameter.

The prognostic factors that are relevant for the success rate of conventional treatment in patients with HD are (according to the German Hodgkin Study Group) (Hasenclever and Diehl, 1998):

- A: Large mediastinal mass (1/3 of maximum thoracic diameter or more)
- B: Extranodal disease
- C: Elevated erythrocyte sedimentation rate
- D: Three or more lymph node areas involved

Low risk (“early-stage favorable) includes stages I and II without risk factors, intermediate risk (“early-stage unfavorable) stages I and II with one or more risk factors. High risk (“advanced stage”) includes stages III and IV as well as stage IIB with risk factors A/B.

Conventional therapeutic strategies for patients with HD include radiation, polychemotherapy, combined modality approaches and high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) (Fuchs et al., 2006, Cashen and Bartlett, 2008). HD is a very radio- and chemotherapy sensitive malignancy. Curative radiotherapy is performed in patients with low-risk. Radiotherapy for HD patients is applied as “involved-field radiation”, “extended-field radiation”, mantle field and inverted Y. Subtotal and total nodal radiation has been frequently used in the 70´s and 80´s of the last century, but is not being performed any more. However, treatment results with radiotherapy alone were disappointing with 10-year-survival rates of about 60%. Many patients suffered a relapse. Therefore, clinical studies were initiated to test whether the addition of chemotherapy is beneficial to these patients. Cytotoxic agents used in the treatment of HD belong to different classes: alkylating agents, vincaalcaloids, anthracyclins and topoisomerase-II-inhibitors. Currently, the ABVD regimen is the gold standard for treatment of HD. It consists of the four drugs adriamycine, bleomycin, vinblastine, and dacarbazine. Indeed, combined modality treatment – radio- and chemotherapy - was able to improve survival rates up to 90% and has become the gold standard not only for these patients but also for those in the “early-stage unfavorable” risk group.

The BEACOPP regimen (bleomycin, etoposide, adriamycine, cyclophosphamide, oncovin, procarbacin and prednisone) has been developed by

the German Hodgkin Study Group for advanced stages and shows better results than standard therapies with disease-free survival of 85% at 82 months (Diehl and Behringer, 2006). However, the long term complications including therapy-related leukaemia are not well documented yet.

Despite the availability of highly effective regimens, some patients will progress or relapse after initial therapy. These patients will require salvage therapy and therefore proceed to ASCT. High-dose chemotherapy, for example with BEAM (carmustin, etoposide, cytarabin and melphalan) followed by autologous stem cell transplantation is reserved for patients with relapsed disease, for non-responders and for those, who achieved only a partial remission following initial polychemotherapy or combined modality approaches. The purpose of this approach is to eradicate malignant cells by an intensified treatment. However, as an unavoidable side effect, normal haematopoietic cells are destroyed, too, necessitating autologous transplantation. In this setting, the patient's haematopoietic stem cells are harvested prior to the transplantation procedure and stored in liquid nitrogen. Immediately after conditioning (i.e. the high-dose therapy itself) stored cells are thawed and reinfused. After several weeks of stem cell expansion in the bone marrow, differentiation to mature blood cells occurs leading to normal peripheral blood counts and reinitiating of the immune system.

1.5 Historical perspective of t-MDS/t-AML in patients treated for lymphomas

In the course of this systematic review, we were also interested in the first reports on leukaemia following therapy of a primary lymphoma. In 1926, a review by Evans and Leucutia described three cases of lymphatic leukaemia following deep Roentgen-therapy of a lymphosarcoma (Evans and Leucutia, 1926). However, leukaemias at that time were classified on morphologic basis only and therefore, it is difficult to distinguish whether these "leukaemias" were truly therapy-induced (myeloid) leukaemias or rather represent a leukaemic phase of the primary, lymphomatous disease. This is corroborated by the fact, that the latency period was rather short ranging from three to six months. Based on these findings, the suspicion arose that all

lymphosarcomas would terminate in a lymphatic leukaemia if life is sufficiently prolonged. A possible etiologic connection between cytotoxic treatment and secondary leukaemia, hence therapy-related leukaemia, has been stated a decade later by Kato and Brunschwig (Kato and Brunschwig,1933). In 1954, E. Beutler reported the development of AML in a patient with reticulum cell lymphoma. He stated that exposure to ionizing radiation is likely an alternative to chance occurrence in this individual (Beutler,1953).The first clinical study to address this question was performed by Newman in 1970 (Newman et al., 1970), who studied 1500 cases of HD and found a significant elevated risk of myelomonocytic leukaemia in treated patients compared to the general population and mentioned that these cases of leukaemia are likely related to the therapy of HD.

t-MDS/t-AML represent one of the severest treatment complications in patients cured of HD (Hake et al., 2007, Kollmannsberger et al., 1998). The incidence of t-MDS/t-AML in this cohort of patients varies widely depending on the dose and duration of the initial treatment, which chemotherapy agents were used, and whether combined radio-/ chemotherapy or salvage therapy including ASCT was performed. t-MDS/t-AML usually arise within the first ten years (median: five years) following initial therapy. After ten years, however, the risk seems comparably to the normal population (Thirman and Larson, 1996).

1.6 Aim of the review

Different studies on t-MDS/t-AML after HD showed an incidence after conventional therapy that is comparable to ASCT, whereas others report a significant increase of t-MDS/t-AML for patients who underwent ASCT (Darrington et al., 1994).The specific aim of this systematic review was to determine the incidence of t-MDS/t-AML for HD patients, who either have received conventional therapy or were treated with high-dose therapy followed by ASCT. The necessity of performing such a review is further corroborated by the fact, that the number of long-term HD survivors is still increasing and ASCT is being used more frequently.

The two possible outcomes of this systematic review are: 1.The incidence of t-MDS/t-AML after high-dose therapy and ASCT is significantly higher than after conventional therapy. This would indicate that drug/radiation dosage plays a major role in the pathogenesis of t-MDS/t-AML. Therefore, alternative first-line strategies should be discussed in order to reduce the number of patients necessitating ASCT.
These alternative strategies may include risk-adapted first line regimens or experimental antibodies. A step in this direction was already undertaken by the introduction of the BEACOPP regimen as first-line treatment approach for high-risk HD patients. 2. The incidence of t-MDS/t-AML after conventional therapy is comparable to ASCT. This would strengthen the hypothesis that certain patients treated with cytotoxic drugs or radiation show “hyperresponsiveness” to these therapies, most likely due to endogenous (genetic) factors. However, even if ASCT is associated with a higher t-MDS/t-AML incidence, genetic risk factors as determinants of these secondary complications cannot be ruled out.

2 MATERIAL AND METHODS

In order to find adequate answers to our question it was important for us to obtain all relevant studies to get a clear and consistent picture of this topic. Initially, we were confronted with the problem that narrative reviews only provide a low level of evidence. This is due to the fact that these reviews usually do not assess the quality of original studies and do not state the extent to which scientific methods have been used to minimize bias. Furthermore, narrative reviews often do not describe how the reviewers have searched, selected and appraised the studies. As a large body of primary studies with disparate findings and substantial uncertainty exists with respect to our question, a systematic review seemed appropriate for us to come up with a conclusion as accurate, stable and unbiased as possible.

Systematic review	Narrative review
• systematic methods used to control bias	**• subjective and potentially biased**
• uses rigorous scientific methodology to search literature	**• no explicit methods for searching literature or reporting of results**
• can be replicated	**• cannot be replicated**

Table 3: Features of a systematic and a narrative review.

2. 1 What is a systematic review?

A systematic review is a literature review of all relevant studies that address a specific clinical question. This scientific investigation uses defined strategies in order to identify, select, appraise and synthesis original articles. Summarizing all results of primary studies that fulfil the inclusion criteria is the only way to limit bias and random error. It is of utmost importance to report precisely all information obtained in this way (Moher and Tsertsvadze, 2006, Crowther and Cook, 2007).

2.1.1 The role of meta-analysis

Meta- analysis was defined by Glass (1976) to be “the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings”. In other words, meta- analysis offers a quantitative summary of the results of a systematic review. As a prerequisite, a well conducted systematic review is absolutely necessary to perform a valid meta-analysis.

2.2 The process of a systematic review

This systematic review was performed according to guidelines described by the Cochrane Handbook and the QUOROM (**QU**ality **O**f **R**eporting **O**f **M**eta-analysis) statement (Moher et al., 2000).

2.2.1 Steps of a systematic review

1) Formulating the problem
2) Locating and selecting studies
3) Critical appraisal of studies
4) Collecting data
5) Analysing and presenting results
6) Interpreting results
7) Improving and updating reviews

2.2.2 Formulation of the clinical problem

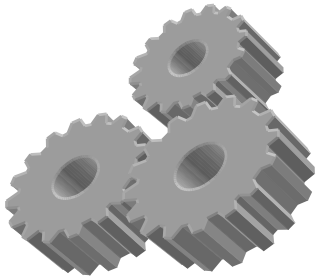
The first step was to define an explicit clinical question: we were interested in a specific population (all patients with HD), a specific long-term complication (t-MDS/t-AML), exposure to a specific treatment (conventional radio-/ chemotherapy versus ASCT) and the incidence of this specific long-term complication in either treatment group. Therefore the question of this systematic review is: The incidence of therapy-related myelodysplastic syndrome and acute myeloid leukaemia after conventional therapy or autologous stem cell transplantation in patients with Hodgkin's disease.

2.2.3 Locating studies

The next step was the systematic literature search for primary studies. This thorough search included electronic databases (Medline, EMBASE and Cochrane Library) and conference proceedings (American Society of Hematology, European Haematology Association and American Society of Clinical Oncology). In addition, reference lists of selected publications and previously published reviews were screened to identify relevant studies. In order to perform a search as effective as possible, we used several different search terms and all possible combinations (*Figure 3*).

Hodgkin's disease
Hodgkin's lymphoma
lymphogranulomatosis

treatment related
treatment associated
treatment induced
therapy related
therapy associated
therapy induced
secondary



acute myeloid leukaemia
acute myelogenous leukaemia
AML
myelodysplasia
myelodysplastic syndrome
MDS

Figure 3: Search terms used and their combinations

2.2.4 Selection process

Each single abstract and each preselected original article was assessed for fulfilling the eligibility criteria.

1) We only included studies published in English.
2) Only peer-reviewed papers were included which guaranteed a certain quality level. Abstracts or dissertations were excluded.
3) Potentially relevant papers had to include a median follow-up of at least five years reflecting the median latency period of t-MDS/t-AML. Otherwise too many events would not have been recognised.
4) Standardized therapy-protocols had to be listed in order to assign late complication to a specific treatment regimen.
5) In case of several publications, only the latest and most informative study of each author and institution was included.

6) A minimum of 20 HD patients had to be included into the study to fulfil our inclusion criteria.

2.2.5 Appraisal of identified studies

All original articles between January 1970, when the first study of t- MDS/t-AML following HD was published (Newman et al., 1970), and March 2008 were identified. Abstracts of these articles were screened for fulfilling the inclusion criteria. Of those selected, the full text was retrieved in order to check all inclusion criteria. If essential data were missing, we contacted the corresponding authors by email. Finally we had to decide, which papers are going to be definitely included in this work.

2.3 Study protocol

Here is a short synopsis of the study protocol and which data we have collected: the first author of the study; the institution, where the study was performed; the study period; the study design, whether it was a cohort study or a randomized controlled trial. A cohort study is a form of longitudinal study dealing with a well characterized group of patients. With respect to this systematic review, a cohort refers to either the group of conventionally treated patients of those undergoing ASCT. Either cohort is observed for at least five years for the occurrence of t-MDS/t-AML. A randomized clinical trial compares two or more different treatment strategies randomly allocated to patients sharing certain clinical features. In our case, patients with HD and a high-risk profile would be randomly allocated to either conventional therapy or ASCT. Randomized controlled trials provide the highest level of evidence. We also distinguished whether the incidence of t-MD/t-AML is the primary end point of the author's investigation (A) or is the "by-product" of a study that primarily investigates the efficacy and efficiency of a certain treatment schedule for HD (B). We further assessed the number of patients undergoing ASCT and conventional therapy; the kind of conventional therapy and the number of treatment regimens applied; the median as well as maximum follow up; the latency period, the time from

start of initial treatment to the diagnosis of t-MDS/t-AML; the age of the study population: median, minimum, maximum, mean and standard deviation; and finally, the crude, actuarial and cumulative incidence.

3 RESULTS

We identified a total of 3266 potentially relevant studies using the search terms listed in *Figure 3*. The abstracts were screened for inclusion criteria in order to identify those articles, which may get included in our analysis. *Figure 4* shows the steps taken to select the appropriate studies. A total of 3175 had to be excluded due to not fulfilling our selection criteria. We then retrieved the full-text of the remaining 91 potentially appropriate studies. Each single paper was assessed and when faced with missing data, we tried to obtain this information by contacting the corresponding author. In this step, thirteen papers had to be excluded for missing data. Of the remaining 78 papers, 22 were excluded due to data duplication. Finally, a total of 56 papers fulfilled the inclusion criteria and were used in this systematic review.

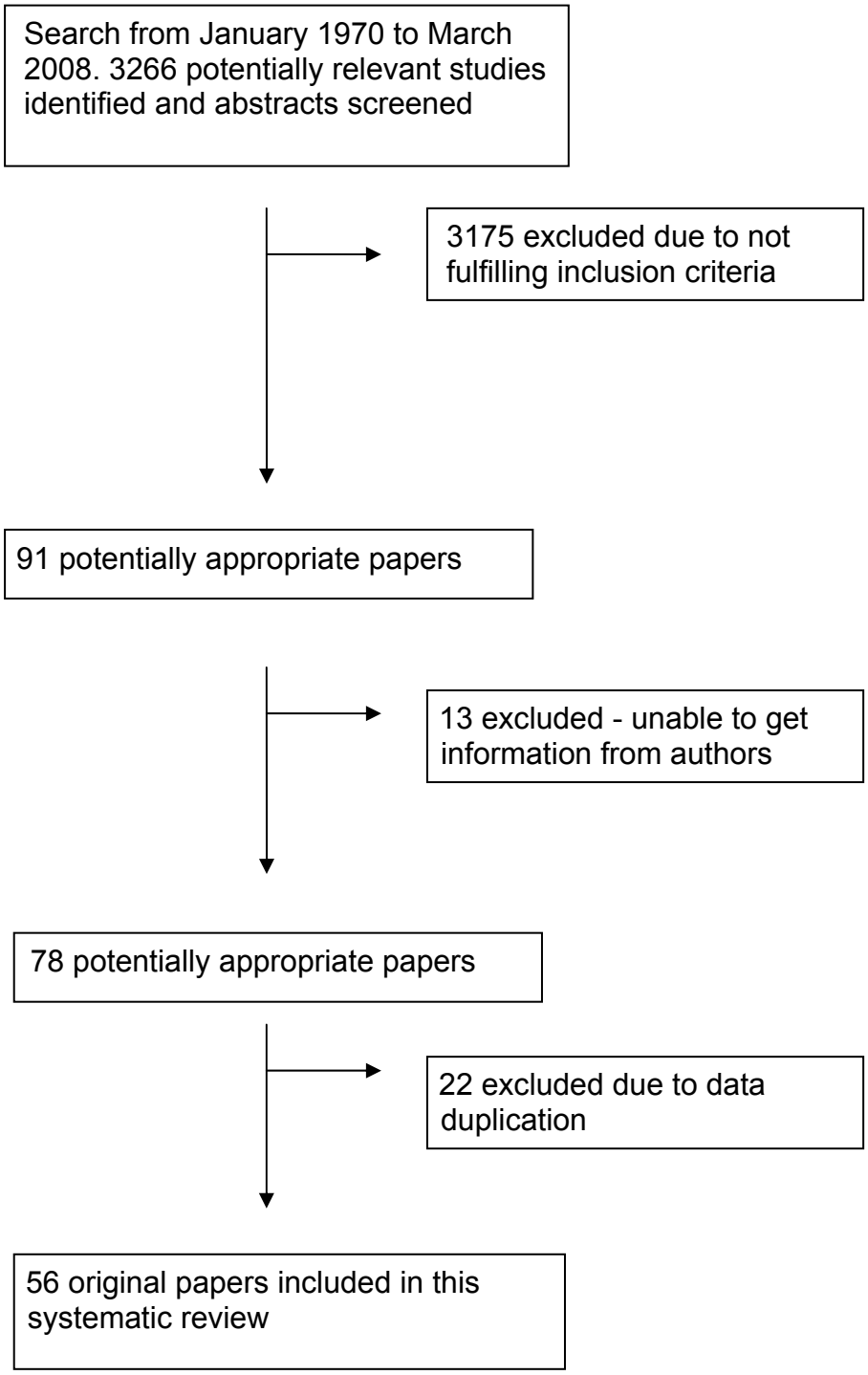


Figure 4: QUOROM flowchart illustrating in detail the retrieved articles.

A total of 30.607 patients´ data, collected from 56 relevant studies, were entered into our systematic review. The data shown in *Tables 4 and 5* are: the publication (first author), the study period, the study design (cohort study, CS, versus randomized controlled trial, RCT), the primary goal of the study (A versus B, see above), median follow-up of the study, median age of the patients, conventional therapy (CT, chemotherapy; RT, radiotherapy; CRT, combined modality treatment), the number of t-MDS/t-AML cases and total number of cases and finally, crude, actuarial and cumulative incidences. Additionally, for patients undergoing ASCT, we listed the pre-ASCT therapy and the type of conditioning (i.e. high-dose therapy immediately prior to transplantation).

Out of the 56 studies, there were 55 cohort studies and only one randomized controlled trial. Forty-nine cohort studies dealt with conventional therapy whereas six cohort studies reported on ASCT. In 30 of 56 studies (53%), the primary endpoint was t-MDS/t-AML incidence (designated “A” in *Tables 4 and 5*). The median/mean patients´ age was stated in 33/56 studies (59%) – six of them reported on paediatric patients aged less than 18 years. The median follow-up ranged between five years (a mandatory inclusion criterion) and 17.8 years. The major type of incidence stated was “crude incidence” which ranged between 0 to 14.8%.

Table 4 shows the characteristics of 50 studies including a total of 29.372 HD patients, who were treated with conventional therapy. In *Table 5,* 1200 patients from 7 studies, who received ASCT for HD, are listed. The smaller number of ASCT studies most likely results from the fact that bone marrow transplantation is a rather new treatment strategy introduced in the 80´s of the last century. The majority of ASCT studies therefore only describe short-term outcome and early complications associated with transplantation. This resulted in a median follow-up often too short for our analysis leading to exclusion of these studies.

t-MDS/t-AML in conventionally treated adult and paediatric patients

44 studies reporting on t-MDS/t-AML after conventional treatment included a total of 26713 adult patients with HD. The trials recruited between 37 and 3981 patients. The earliest study period was from 1949 -1983 and the latest from 1980 - 2001. The median follow-up ranged from five to 17.8 years. In total, 208 cases developed t-MDS/t-AML. The range of the crude incidence of t-MDS/t-AML after conventional radiochemotherapy is between 0 and 5.4%. Three studies have reported no cases of t-MDS/AML among a total of 299 patients. Studies exploring patients treated exclusively with either chemotherapy or radiation provided a crude incidence of t-MDS/t-AML for those treated with chemotherapy alone from 0 to 6.3% and from 0 to 3.5% for those patients undergoing radiotherapy only. Four chemotherapy and six radiation studies have reported no t-MDS/t-AML events. Taken the twelve studies with a median follow–up of more than 10 years separately into account, one can clearly see that the crude incidence is not increasing (range between 0.65 and 5.2%). This underscores the fact that the risk of developing t-MDS/t-AML peaks at 5 years and approaches normal values ten years after initial therapy. The actuarial incidence - stated in nine publications - ranges between 0.75 and 5.9 in studies with a median follow-up of more than 10 years. The latency period, i.e. the time from initiation of therapy to the diagnosis of the secondary malignancy, ranges from 3.0 to 8.1 years.

We were also able to include six paediatric studies including a total of 2659 patients that were treated with radiochemotherapy. Thirty-two t-MDS/t-AML events were reported. The crude incidence ranged from 0.75% (Schellong et al., 1997) to 3.6% (Donaldson and Link, 1987). The studies reporting cases of t-MDS/t-AML had a median follow-up from 6.8 to 15.1 years.

t-MDS/t-AML after ASCT

Out of 1200 patients enrolled into seven ASCT studies, 30 developed t-MDS/t-AML reflecting a crude incidence of 2.5%. The included trials enrolled between 27 and 595 patients, the range of the median follow-up is 5 to15 years. For the group of ASCT patients, the range of the crude incidence of t-MDS/t-AML is between 1.9%

and 14.8%. There were no trials without any cases of t-MDS/t-AML. The latency period for transplanted patients to develop t- MDS/t-AML is between 1.0 and 6.6 years. However, some studies have not stated whether this was calculated from the time of transplantation or the start of the initial therapy. There was only one randomized study comparing conventional treatment and ASCT showing a crude incidence of t-MDS/t-AML of 0.9 and 2%, respectively. The actuarial incidence was listed in only one study in the ASCT arm and is 1.9% at ten years.

Table 4. t-MDS/ t-AML after conventional therapy for HD

Publication	Study Period	Design	Median Follow-up (yr)	Median age (yr)	therapy	No. of Cases/ No. of Treated Patients	Incidence (%)	
							Crude	Actuarial
Aleman	65-87	CS, B	17,8	26	CT+/-RT	21/1261	1,67	
Andrieu	4/72-5/80	CS, A	10,5#	27,5	CRT	10/441	2,27	3,5 at 15yr
Beaty	62-93	CS, A	9	13,5	RT/CT/CRT	4/499	0,8	
Brusamolino	75-92	CS, A	10	34	RT/CT/CRT	36/1659	2,17	4.2 at 15yr
Cornbleet	1/68-12/80	CS, B	7,4	26	RT/CT/CRT	1/108	0,93	
Cimino	1/69-12/79	CS, A	10,5	NR	RT/CT/CRT	23/974	2,36	2,8 at 10yr
Anselmo	2/83-10/91	CS, B	9,2	31	RT/CRT	4/218	1,83	
Cramer	4/72-5/80	CS, B	6,8	16	CRT	1/ 72	1,39	
Delwail	72-88	CS, A	9,1	28	CRT	11/761	1,45	
Duggan	NR	CS, B	6	28	CT	13/852	1,53	
Donaldson	70-83	CS, B	7,5	10	CRT	2/ 55	3,64	11at 10yr
Glick	1/87-7/89	CS, B	7,3	30,7	CT+/-RT	10/691	1,45	
Hudson	68-90	CS, B	15,1	14,4	CT+/-RT	4/387	1,03	
Koletskey	69-82	CS, A	8,3	NR	RT/CT/CRT	5/183	2,73	1,5 at 5yr; 5,9 at 10yr
Kushner	49-83	CS, A	9	28,5	CT+/-RT	5/254	1,97	
Chow	5/87-12/97	CS, A	8,5	NR	RT/CT/CRT	0/111	0	
Longo	5/78-10/88	CS, B	7,7	28,5	CT	4/125	3,2	
Mauch	4/69-7/77	CS, B	5,4	28,5	CT+/-RT	1/ 83	1,2	
Nelson	1/60-6/77	CS, A	6	31	RT/CT/CRT	1/248	0,4	
Ng	4/69-12/97	CS, A	12	NR	RT/CT/CRT	23/1319	1,74	
Olver	68-79	CS, B	10,2	25	CT+/-RT	4/161	2,48	
Schellong	6/78-9/90	CS, A	8,3	12	CT+/-RT	5/667	0,75	0,7at 10yr; 1,1at 15yr
Swerdlow	63-91	CS, A	9,1#	NR	CT	13/1039	1,25	
Viviani	9/90-3/93	CS, B	5,6	27	CT+/-RT	0/73	0	

Table 4, cont´d. t-MDS/ t-AML after conventional therapy for HD

Publication	Study Period	Design	Median Follow-up (yr)	Median age (yr)	therapy	No. of Cases/ No. of Treated Patients	Incidence (%)	
							Crude	Actuarial
Santoro, Viviani	2/71-2/83	CS, B	7,4	35	CT+/-RT	6/122	4,92	
Santoro	9/74-7/82	CS, B	7	27	CT+/-RT	2/232	0,86	
Bonfante	9/76-6/82	CS, B	10	35	CT+/-RT	7/201	3,48	
Vlachaki	67-87	CS, A	16,5	31	CT+/-RT	2/145	1,38	
Vassilakopoulos	7/80-12/01	CS, B	7	33	CRT	8/368	2,17	
Tucker	68-85	CS, A	5	31	RT/CT/CRT	27/1507	1,8	
Faria	78-88	CS, B	6,7#	30	RT/CT/CRT	2/37	5,41	
Meadows	55-79	CS, A	7	12	CT+/-RT	16/979	1,63	
Mendenhall	10/64-4/84	CS, A	11	NR	RT/CRT	5/200	2,5	
Cellai	60-91	CS, A	10,7#	NR	RT/CT/CRT	17/1524	1,12	
Hancock	3/67-9/80	CS, B	14	NR	RT/CRT	6/326	1,84	
Aisenberg	7/67-6/81	CS, A	7,5	NR	CT+/-RT	8/408	1,96	4,9 at 12yr
Coltman	1/71-8/78	CS, A	10	NR	RT/CT/CRT	17/659	2,58	
Blayney	64-75	CS, A	15,3	NR	CT	10/192	5,21	
Henry-Amar	64-71	CS, A	10	NR	RT/CRT	3/334	0,89	
Tawil	69-77	CS, A	7,2	NR	RT/CT/CRT	4/227	1,76	
Zinzani	1/70-12/84	CS, A	12	NR	RT/CT/CRT	14/552	2,53	
Sont	1/69-12/88	CS, A	6#	NR	RT/CT/CRT	6/482	1,24	
v.d.Velden	72-78	CS, A	5,5	NR	RT/CT/CRT	18/1681	1,07	
Selby	1/75-3/86	CS, B	7,6	NR	CT+/-RT	2/284	0,7	2,7 at 10yr
Aviles	83-88	CS, B	11,35	43	RT/CT/CRT	2/307	0,65	
Anderson	10/74-8/81	CS, B	10,9	NR	RT/CRT	0/115	0	
Lavey	1/70-9/81	CS, A	7,5	31,5	RT/CT/CRT	4/313	1,28	
Pedersen-Bjergaard	1/70-1/81	CS, A	5,5	NR	CT+/-RT	20/391	5,12	
Forrest	1/76-12/01	RCT, A	9,7	29	CT+/-RT	14/1530	0,92	
Harrison	9/89-5/95	CS,A	5	NR	CT	77,1% of 35/3981	NR	0,8% at 10yr

#mean follow up; NR: not reported

Table 5. t-MDS/ t-AML after Autologous Stem Cell Transplantation for HD

Publication	Study Period	Design	Median Follow-up (yr)	Median age (yr)	Pre-ASCT Therapy	Conditioning	No. of Cases/ No. of Treated Patients	Incidence (%)	
								Crude	Actuarial
Akpek	3/85-4/98	CS, B	5,1	30	CT+/-RT	Bu,Cy,Eto,TBI	3/104	2,88	
Forrest	1/76-12/01	RCT, A	9,8	28,77	CT+/-RT	Cy/Eto/Carm/var	4/202	1,98	
Pedersen-Bjergaard	1/91-7/95	CS, B	15	NR	CT+/-RT	BEAM	4/27	14,81	
Tarella	1/93-9/00	CS, B	5	32	CT	L-PAM,BEAM	5/92	5,43	
Bierman	9/78-12/87	CS, B	6,4	NR	CT+/-RT	CBV	5/128	3,9	
Taylor	5/84-10/95	CS, A	5,1	28	CT+/-RT	Melphalan/Eto	1/52	1,92	
Harrison	9/89-5/95	CS, A	5	NR	CT	BEAM	22,9% of 35/595	NR	1,9% at 10y

4 DISCUSSION

Hodgkin's disease is one of those human malignancies with the highest cure rates. The majority of patients is cured with first-line multiagent chemotherapy combined with radiation. These strategies are now risk-adapted providing sufficient tumor control to high-risk patients and avoiding unnecessary toxicity to those with low-risk disease. In this way, 80% – 90% of patients with HD achieve a complete remission as a prerequisite for long-term survivorship (Borchmann et al., 1998). In the remaining 10 -20% of patients with resistant or relapsed HD, high-dose therapy followed by autologous stem cell transplantation is still able to achieve these goals in roughly half of all cases.

However, as patients survive HD, long-term consequences of cytotoxic therapies become apparent. Among those, therapy-related myelodysplastic syndrome and acute myeloid leukaemia are one of the severest. These secondary myeloid malignancies are diagnosed after a median latency time of three to five years and present with signs and symptoms of bone marrow failure (Thirman and Larson, 1996). Cytogenetic analysis of neoplastic cells exhibit chromosomal aberrations to a high degree (Pagana et al., 2001).The prognosis of patients with t-MDS/t-AML is poor showing a 5-year survival rate of less than 10% (Thirman and Larson, 1996). Allogeneic stem cell transplantation is regarded as the only curative option. As the number of patients becoming long-term survivors after a primary malignancy is increasing, a concomitant increase of t-MDS/t-AML is being observed.

4.1 Incidence of t-MDS/t-AML

The topic of this systematic review was the incidence of t-MDS/t-AML after conventional therapy and ASCT for HD. However, before discussing our results, types of measures of incidence should be mentioned briefly. Crude incidence is calculated as the number of events divided by the number of patients who entered the study. However, crude incidence underestimates the true incidence, because

with additional follow up the number of patients at risk decreases as patients die due to the primary malignancy or unrelated causes like myocardial infarction, trauma etc. Another type of incidence measure is the actuarial incidence, which is calculated according to the Kaplan Meier method. However, patients also die of other causes ("competing risks") leading to overestimation of the "true" incidence of t-MDS/t-AML. Therefore, the Kaplan-Meier method is inappropriate for estimation purposes in the presence of competing risks. Cumulative incidence incorporates competing risk factors. It estimates the cumulative probability of an event having occurred in the presence of other competing events. This type of analysis is also called competing risk analysis or absolute cause specific risk analysis. So, cumulative incidence is the best parameter to assess the frequency of a secondary event (t-MDS/t-AML) in the presence of a competing risk (in this study most likely death due to HD or toxicity of cytotoxic therapies) (Armitage et al., 2003, Travis, 2007, Gooley et al., 1999, Dignam and Kocherginsky, 2008).

Nevertheless, the most frequently used measure of incidence in the 56 studies retrieved was the crude incidence. Actuarial incidence was stated in 10/56 studies and cumulative incidence was not mentioned at all. In conventionally treated HD patients, the crude incidence was between 0 and 5.4% whereas in the ASCT group, it ranged between 1.9 and 14.8%. Actuarial incidences were stated in the conventional therapy group with values as high as 5.9% at 10 years. Although no statistical analysis ("meta-analysis") was performed, these data indicate that the incidence of t-MDS/t-AML is higher in the ASCT group. At this point, it would be interesting to perform subgroup analyses in order to identify factors influencing risk to t-MDS/t-AML. These data should provide information whether the transplant process itself – consisting of stem cell purging and pre-ASCT high-dose therapy – contribute to the higher risk or repeated courses of conventional chemo-/ radiotherapy applied before. As already outlined, ASCT in HD patients is not performed "up-front" but used as a salvage therapy for those with relapsing or resistant disease. Unfortunately, information on the number of therapy regimens is scarce throughout the articles used for this systematic review precluding such analyses. This question was also addressed in a few original articles published previously (Pedersen-Bjergaard et al., 1997, Harrison et al., 1999) and the authors uniformly come to the conclusion, that cumulative toxicity is the most relevant issue for t-MDS/t-AML leukaemogenesis.

Other risk factors are the use of total body irradiation (TBI) – mainly as part of the conditioning regimen – and age. With respect to the former one, only one ASCT study has included TBI. With respect to age, a comparison of adult and paediatric studies might be a rough indicator of the value of this risk factor. Whereas the crude incidence of t-MDS/t-AML was as high as 5.4% in adult studies, it was 3.6% in paediatric ones. Taken together, incidence of t-MDS/t-AML varies widely between studies dealing with conventional therapy as well as between studies of ASCT for HD patients. The group of ASCT patients shows higher incidences indicating a role for toxicity in the pathogenesis of these myeloid neoplasms.

4.2 Predisposition

As outlined, toxicity is of importance for secondary leukaemogenesis. Therefore, the question arises on the role of genetic predisposition. Evidence is accumulating that “endogenous” factors also contribute to the development of t-MDS/t-AML. Why do a small, but significant proportion of patients receiving cytotoxic therapies, develop a (pre-)leukaemic condition? Clinical insight is obtained from rare, hereditary disorders. Patients with neurofibromatosis 1, who have a germline mutation in one allele of the *NF1* gene, are at increased risk of de novo leukaemias as well as t-MDS/t-AML. (Maris et al., 1997) Similar results were published for patients with Noonan-syndrome harbouring germline mutations in *C-RAF*, *PTPN11* or *SOS1* (Seedhouse and Russell, 2007)

Interesting data came from molecular studies investigating the role of genetic polymorphisms in the pathogenesis of t-MDS/t-AML(Felix et al., 1998) They have focused on genes mediating two major functions associated with cytotoxic drugs: 1st, genes involved in drug metabolism and 2nd, genes involved in DNA repair. Drug metabolism is a process of biochemical modification or degradation of substances through specialized enzymatic systems. These are important steps determining the duration and intensity of the pharmacological action of given drugs. The cytochrome P450 monooxygenase system is one of the most important pathways in this regard.
Genetic polymorphisms - i.e. genetic variants that appear in at least 1% of the population - account for some variability regarding the specific effects of drugs.

Polymorphisms associated with altered t-MDS/t-AML risk are described within the NQO1, CYP3A4 and GST1 genes, respectively.(Seedhouse et al., 2002)

The main mode of action of cytotoxic therapies is mediated by DNA damage leading to apoptosis preferentially of neoplastic cells. Therefore, polymorphisms within DNA repair genes are attractive candidates to be studied. A polymorphism within MSH2, involved in DNA mismatch repair, within XRCC1, crucial for base excision repair, within XPD, a nucleotide excision repair gene and within RAD51, encoding a homologous repair protein, have all been associated with t-MDS/t-AML leukaemogenesis.

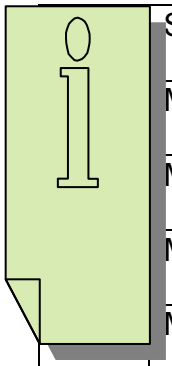
4.3 Limitations

For the clinical question addressed it would have been desirable to perform a meta-analysis. In this way we could have assessed the impact of either therapy directly. However, this was not possible as only one randomized controlled trial fulfilled our strict inclusion criteria.

Limitation of the original studies also became limitations of our systematic review. A problem that we frequently faced was the fact that the cumulative incidence was not stated in any article. So we had to rely on crude incidence only, well knowing that this underestimates the true risk of t-MDS/AML in HD patients. Another problem we had to deal with was the follow-up period which was not stated in several articles otherwise fulfilling our inclusion criteria and describing a large cohort of patients. Therefore, we contacted corresponding authors asking for this madatory information. There was a response rate of 30 %. The inhomogeneity of study populations was also difficult to deal with. For example, some studies were designed as survivor studies analyzing patients from time X (often years) after cessation of a specific treatment. This type of study does not take into account the number of events and the number of deaths that occurred previously. For this reason, “survivor studies” had to be excluded.

Possibly the greatest limitation for our work was the lack of information regarding the number of regimens given in the conventional treatment group and pre-transplant in the ASCT group. So the burning question whether t-MDS/t-AML observed after stem cell transplantation is really a complication of the transplant procedure itself or a consequence of prior extensive radio- and chemotherapy remains largely unanswered.

Knowledge of these limitations should prompt authors of future studies on t-MDS/t-AML to include indispensable data for a reliable assessment of risk factors. Therefore, we would finally like to propose a list of data which we regarded as mandatory to pursue this goal:



	Study period
	Median follow-up from time of diagnosis of the primary disease
	Median latency period from first cytotoxic therapy
	Median latency period from ASCT
	Median and mean age at first treatment
	Median and mean age at diagnosis of t-MDS/t-AML
	Number of cytotoxic therapies pre-ASCT
	Cumulative doses of chemo- and radiotherapy
	Stem cell mobilisation regimen +/- G-CSF
	Conditioning for ASCT
	Crude incidence of t-MDS/t-AML
	Cumulative incidence t-MDS/t-AML

4.4 Outlook

This systematic review shows that cumulative toxicity plays a significant role in the pathogenesis of t-MDS/t-AML. There are at least a few possibilities how to deal with this problem. One strategy is to further aim at identifying individuals with HD which are at risk of conventional treatment failure. These patients might be candidates for experimental therapies. Monoclonal antibodies like the anti-CD20 antibody rituximab or the anti-CD30 antibody, directed against the Reed-Sternberg specific CD30 antigen, are already being explored. These efforts would lead to a reduction of both, treatment failure for HD and development of t-MDS/t-AML. Novel tools like gene expression profiling could aid in identifying such patients. Another option is to further explore genetic risk factors associated with increased t-MDS/t-AML risk. Knowledge about genetic susceptibility to t-MDS/t-AML may open the possibility to assess the risk of secondary myeloid neoplasms already at the time, before treatment for HD has been commenced. In these cases, a careful discussion should be initiated to assess the benefit and risk of alternative strategies.

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6 Appendix

Basic information on articles dealing with conventional therapy:

Author	(Aleman et al., 2003)
Study design	CS,B
Study group	1261
Median follow-up(mo)	213
Latency period(y)	6
Cases of t-MDS/t-AML	21

Author	(Andrieu et al., 1990)
Study design	CS,A
Study group	441
Median follow-up(mo)	126
Latency period(y)	4,5
Cases of t-MDS/t-AML	10

Author	(Beaty et al., 1995)
Study design	CS,A
Study group	499
Median follow-up(mo)	108
Latency period(y)	4
Cases of t-MDS/t-AML	4

Author	(Brusamolino et al., 1998)
Study design	CS,A
Study group	1659
Median follow-up(mo)	120
Latency period(y)	5
Cases of t-MDS/t-AML	36

Author	(Cornbleet et al., 1985)
Study design	CS,B
Study group	108(108RTX)
Median follow-up(mo)	88
Latency period(y)	6
Cases of t-MDS/t-AML	1

Author	(Cimino et al., 1991)
Study design	CS,A
Study group	947
Median follow-up(mo)	126
Latency period(y)	4,8
Cases of t-MDS/t-AML	23

Author	(Anselmo et al., 1998)
Study design	CS,B
Study group	218
Median follow up (mo)	110
Latency period (y)	NR
Cases of t-MDS/t-AML	4

Author	(Cramer and Andrieu, 1985)
Study design	CS,B
Study group	72(72CRTX)
Median follow-up(mo)	28
Latency period(y)	NR
Cases of t-MDS/t-AML	1

Author	(Delwail et al., 2002)
Study design	CS,A
Study group	761(761CRTX)
Median follow-up(mo)	109,2
Latency period(y)	NR
Cases of t-MDS/t-AML	11

Author	(Duggan et al., 2003)
Study design	CS,B
Study group	852(852CTX)
Median follow-up(mo)	72
Latency period(y)	NR
Cases of t-MDS/t-AML	13

Author	(Donaldson and Link, 1987)
Study design	CS,B
Study group	55(55CRTX)
Median follow-up(mo)	90
Latency period(y)	5
Cases of t-MDS/t-AML	2

Author	(Glick et al., 1998)
Study design	CS,B
Study group	691(597CTX;94CRTX)
Median follow-up(mo)	87,6
Latency period(y)	NR
Cases of t-MDS/t-AML	10

Author	(Duggan et al., 2003)
Study design	CS,B
Study group	852
Median follow-up(mo)	72
Latency period(y)	NR
Cases of t-MDS/t-AML	11

Author	(Koletsky et al., 1986)
Study design	CS,A
Study group	183(183CRTX)
Median follow-up(mo)	99,6
Latency period(y)	NR
Cases of t-MDS/t-AML	5

Author	(Kushner et al., 1988)
Study design	CS,A
Study group	254
Median follow-up(mo)	108
Latency period(y)	4,2
Cases of t-MDS/t-AML	5

Author	(Chow et al., 2006)
Study design	CS,A
Study group	111
Median follow-up(mo)	102
Latency period(y)	NR
Cases of t-MDS/t-AML	0

Author	(Longo et al., 1991)
Study design	CS,B
Study group	125(125CTX)
Median follow-up(mo)	92,4
Latency period(y)	NR
Cases of t-MDS/t-AML	4

Author	(Mauch et al., 1983)
Study design	CS,B
Study group	83(62RTC,21CRTX)
Median follow-up(mo)	64,8
Latency period(y)	NR
Cases of t-MDS/t-AML	1

Author	(Nelson et al., 1981)
Study design	CS,A
Study group	248(108RTX,140CRTX)
Median follow-up(mo)	72
Latency period(y)	6,6
Cases of t-MDS/t-AML	1

Author	(Ng et al., 2002)
Study design	CS,A
Study group	1319
Median follow-up(mo)	144
Latency period(y)	5,3
Cases of t-MDS/t-AML	23

Author	(Olver et al., 1988)
Study design	CS,B
Study group	161(28CTX,133CRTX)
Median follow-up(mo)	122,4
Latency period(y)	NR
Cases of t-MDS/t-AML	4

Author	(Schellong et al., 1997)
Study design	CS,A
Study group	667(667CRTX)
Median follow-up(mo)	99,6
Latency period(y)	5,3
Cases of t-MDS/t-AML	5

Author	(Swerdlow et al., 1997)
Study design	CS,A
Study group	1039
Median follow-up(mo)	109,2
Latency period(y)	NR
Cases of t-MDS/t-AML	13

Author	(Viviani et al., 1999)
Study design	CS,B
Study group	73(73CRTX)
Median follow-up(mo)	67,2
Latency period(y)	NR
Cases of t-MDS/t-AML	0

Author	(Santoro et al., 1986)
Study design	CS,B
Study group	122
Median follow- up(mo)	88,8
Latency period(y)	NR
Cases of t-MDS/t-AML	6

Author	(Santoro et al., 1987)
Study design	CS,B
Study group	232(232CRTX)
Median follow-up(mo)	84
Latency period(y)	6,1
Cases of t-MDS/t-AML	2

Author	(Bonfante et al., 1992)
Study design	CS,B
Study group	201(116RTX,85CRTX)
Median follow-up(mo)	120
Latency period(y)	NR
Cases of t-MDS/t-AML	7

Author	(Vlachaki et al., 1997)
Study design	CS,A
Study group	145(16CTX,129RTX)
Median follow-up(mo)	198
Latency period(y)	7
Cases of t-MDS/t-AML	2

Author	(Vassilakopoulos et al., 2004)
Study design	CS,B
Study group	368(368CRTX)
Median follow-up(mo)	84
Latency period(y)	6,2
Cases of t-MDS/t-AML	8

Author	(Tucker et al., 1988)
Study design	CS,A
Study group	1507(80CTX,600RTX,827CRTX)
Median follow-up(mo)	60
Latency period(y)	NR
Cases of t-MDS/t-AML	27

Author	(Faria et al., 1996)
Study design	CS,B
Study group	37
Median follow-up(mo)	80,4
Latency period(y)	3
Cases of t-MDS/t-AML	2

Author	(Meadows et al., 1989)
Study design	CS,A
Study group	979
Median follow-up(mo)	84
Latency period(y)	4,5
Cases of t-MDS/t-AML	16

Author	(Mendenhall et al., 1989)
Study design	CS,A
Study group	200(143RTX,57CRTX)
Median follow-up(mo)	132
Latency period(y)	NR
Cases of t-MDS/t-AML	5

Author	(Cellai et al., 2001)
Study design	CS,A
Study group	1524
Median follow-up(mo)	128,4
Latency period(y)	NR
Cases of t-MDS/t-AML	17

Author	(Hancock et al., 1988)
Study design	CS,B
Study group	326
Median follow- up(mo)	168
Latency period(y)	NR
Cases of t-MDS/t-AML	6

Author	(Aisenberg, 1983)
Study design	CS,A
Study group	408(188RTX,220CRTX)
Median follow-up(mo)	90
Latency period(y)	6,3
Cases of t-MDS/t-AML	8

Author	(Coltman and Dixon, 1982)
Study design	CS,A
Study group	659
Median follow-up(mo)	120
Latency period(y)	NR
Cases of t-MDS/t-AML	17

Author	(Blayney et al., 1987)
Study design	CS,A
Study group	192
Median follow-up(mo)	183,6
Latency period(y)	NR
Cases of t-MDS/t-AML	10

Author	(Henry-Amar, 1983)
Study design	CS,A
Study group	334
Median follow-up(mo)	120
Latency period(y)	NR
Cases of t-MDS/t-AML	3

Author	(Tawil and Mercier, 1983)
Study design	CS,A
Study group	227(1CTX,97RTX,129CRTX)
Median follow-up(mo)	86,4
Latency period(y)	NR
Cases of t-MDS/t-AML	4

Author	(Zinzani et al., 1991)
Study design	CS,A
Study group	552(109CTX,115RTX,328CRTX)
Median follow-up(mo)	144
Latency period(y)	3,9
Cases of t-MDS/t-AML	14

Author	(Sont et al., 1992)
Study design	CS,A
Study group	482
Median follow-up(mo)	72
Latency period(y)	NR
Cases of t-MDS/t-AML	6

Author	(van der Velden et al., 1988)
Study design	CS,A
Study group	1681
Median follow-up(mo)	66
Latency period(y)	NR
Cases of t-MDS/t-AML	18

Author	(Selby et al., 1990)
Study design	CS,B
Study group	284(229CTX.55CRTX)
Median follow-up(mo)	92
Latency period(y)	8,1
Cases of t-MDS/t-AML	2

Autho	(Aviles and Delgado, 1998)
Study design	CS,B
Study group	307(99CTX,106RTX,102CRTX)
Median follow-up(mo)	136,8
Latency period(y)	NR
Cases of t-MDS/t-AML	2

Author	(Anderson et al., 1991)
Study design	CS,B
Study group	115(56RTX,59CRTX)
Median follow-up(mo)	131
Latency period(y)	NR
Cases of t-MDS/t-AML	0

Author	(Lavey et al., 1990)
Study design	CS,A
Study group	313
Median follow-up(mo)	90
Latency period(y)	NR
Cases of t-MDS/t-AML	4

Author	(Pedersen-Bjergaard et al., 1987)
Study design	CS,A
Study group	391
Median follow-up(mo)	66
Latency period(y)	NR
Cases of t-MDS/t-AML	20

Author	(Forrest et al., 2005)
Study design	RCT,A
Study group	1530
Median follow-up(mo)	116,4
Latency period(y)	3,5
Cases of t-MDS/t-AML	14

Author	(Harrison et al., 1999)
Study design	CS,A
Study group	3981
Median follow-up(mo)	60
Latency period(y)	NR
Cases of t-MDS/t-AML	77,1 % of 35/3981

***Basic information on articles dealing with autologous stem cell transplantation*:**

Author	(Akpek et al., 2001)
Study design	CS,B
Study group	104
Median follow-up(mo)	66
Latency period(y)	NR
Cases of t-MDS/t-AML	3

Author	(Forrest et al., 2005)
Study design	RCT,A
Study group	202
Median follow-up(mo)	117,6
Latency period(y)	3,5
Cases of t-MDS/t-AML	4

Author	(Pedersen-Bjergaard et al., 1997)
Study design	CS,B
Study group	27
Median follow-up(mo)	180
Latency period(y)	NR
Cases of t-MDS/t-AML	4

Author	(Tarella et al., 2003)
Study design	CS,B
Study group	92
Median follow-up(mo)	60
Latency period(y)	1,6
Cases of t-MDS/t-AML	5

Author	(Bierman et al., 1993)
Study design	CS,B
Study group	128
Median follow-up(mo)	77
Latency period(y)	NR
Cases of t-MDS/t-AML	5

Author	(Taylor et al., 1997)
Study design	CS,A
Study group	52
Median follow-up (mo)	61,2
Latency period(y)	NR
Cases of t-MDS/t-AML	1

Author	(Harrison et al., 1999)
Study design	CS,A
Study group	595
Median follow-up(mo)	60
Latency period(y)	NR
Cases of t-MDS/t-AML	22,9 % of 35/595

7 Curriculum vitae

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