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Secondary acute myeloid leukemia – a single center experience

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Secondary acute myeloid leukemia (sAML) may arise from the previous clonal disorder of hematopoiesis, usually from myelodysplastic syndrome (MDS) or from chronic myeloproliferative neoplasia (cMPN) or after exposure to a leukemogenic agent (previous chemotherapy or radiotherapy, some immunosuppressive drugs or environmental leukemogenic agents). Secondary origin of AML is associated with unfavorable prognosis and it is not considered to be conventionally curable (with the exception of secondary acute promyelocytic leukemia).

The presented study is a retrospective analysis of patients diagnosed and treated at the Department of Hemato-Oncology, University Hospital Olomouc in 1996-2008.

Over that period of time, a total 574 patients with AML were diagnosed. Of those, 430 patients were diagnosed as having primary AML; in 86 patients, sAML transformed from myelodysplastic syndrome and 58 patients were followed or treated for various malignancies or were treated with potentially leukemogenic agents because of non-malignant disorders.

Patients with secondary AML are older and less commonly treated with curative intention than those with primary AML. According to cytogenetic findings, their prognosis is often worse. Complete hematologic remission is achieved with a low probability, relapse of the disease occurs frequently and overall survival is worse in almost all prognostic subgroups. With the exception of secondary acute promyelocytic leukemia, the prognosis of which does not differ from very good prognosis of the primary forms, secondary AML is not considered a conventionally curable disease.

Key words: secondary leukemia, myelodysplastic syndrome, prognosis, chemotherapy, stem cell transplantation

Secondary acute myeloid leukemia (sAML) is defined as a disease which may arise from previous clonal disorder of hematopoiesis, usually from myelodysplastic syndrome (MDS), or from chronic myeloproliferative neoplasia (cMPN) or after exposure to a leukemogenic agent (previous chemotherapy or actinotherapy, some immunosuppressive drugs or environmental leukemogenic agents). The terminology of sAML is ambiguous. Sometimes, secondary AML is described as a disease originating from previous MDS or cMPN only [1]. AML associated with previous cytotoxic therapy is termed therapy-related AML (t-AML) [2].

Secondary AML associated with previous cytotoxic therapy can be classified (according to the leukemogenic agent) into two basic groups with typical cytogenetic and morphological characteristics. The first group is associated with alkylating agent (e.g. cyclophosphamide, melphalan) therapy or actinotherapy. It is characterized by dysplastic changes similar to primary MDS, but the grade of dysplasia is higher in sAML [2]. There is a longer latency between exposition to a leukemogenic agent and the origin of leukemia. Bi- or trilinear cytopenia is observed in peripheral blood. Cytogenetic findings include aberrations of chromosomes 5 and/or 7 or a complex karyotype.

The second group comprises patients who were treated with topoisomerase ll inhibitors (e.g. etoposide, mitoxantrone). There is typically a short period between exposition to the drug and development of sAML. A characteristic genetic change is observed (MLL gene alterations located in chromosome band 11q23) [2, 3].

Myeloid blast crisis of CML is not arbitrarily described as leukemia originating from progression of cMPN, it is considered to be natural evolution of the disease. However, sAML originating from polycythemia vera and myelofibrosis is in fact, from a biological point of view, also blast crisis of the basic disease.

Sometimes, the genesis of secondary AML is uncertain. There is the possibility that MDS is not diagnosed in the early phase or it may be detected in the phase of transformation to

AML and in some (not rare) cases the diagnosis of secondary AML can be controversial (e.g. the history of prolonged cytopenia). In the WHO classification, there is a special category for this type of AML called AML with multilineage dysplasia without previous MDS [4]. The origin of secondary AML in patients with non-malignant hematopoietic disease (e.g. aplastic anemia - AA) is rarely described [5].

The origin of AML as a secondary malignancy is generally considered to be a significant unfavorable prognostic factor [6-8]. Secondary AML is believed not to be a conventionally curable disease (i.e. without allogeneic hematopoietic stem cell transplantation - alloHSCT). The exception are patients with favorable cytogenetic findings - especially with acute promyelocytic leukemia; the secondary genesis of the disease obviously does not worsen the favorable prognosis. On the contrary, the data completely confirm that the disease originating from progression of MDS or cMPN is not conventionally curable.

Naturally, these observations have an influence on the therapeutic point of view. Patients with secondary AML are treated intensively, if possible with respect to their age and comorbidities, allogeneic stem cell transplantation is always discussed. On the other hand, older patients with secondary AML and comorbidities, without an available donor, undergo palliative treatment only.

Methods

This work is a retrospective analysis of patients with secondary AML, who were diagnosed and treated at the Department of Hemato-Oncology, University Hospital Olomouc, in 1996 – 2008 with evaluation of incidence, etiopathogenesis, prognostic factors and treatment results. Also a short case report of a patient with an unusual course of the disease is presented.

Statistics. Standard methods were used for description of our data (i.e. for continuous variables: the median, range, mean and standard deviation; for categorical variables: the distribution of frequencies). The survival curves were estimated using the Kaplan-Meier method [9]. The curves were compared using the log-rank test. The Mann-Whitney test was used for comparison of parameters with non-normal distribution (e.g. age, number of leukocytes at diagnosis) [10], normality of distribution was verified using the Kolmogorov-Smirnov test. The Pearson chi-square test was used for comparison of patient distribution by sex and achievement of complete remission in different subgroups. The Fisher exact test [11] was used for comparison of patient division in different cytogenetic subgroups. In all tests, the statistical significance was set at p=0.05. Data was analyzed using statistical software SPSS v. 15 (SPSS Inc., Chicago, USA).

Results

A total of 574 cases of AML diagnosed in 573 patients were followed at our department in 1996-2008. Of those, 430 (75.0%) patients were diagnosed as having primary AML (i.e. without previous malignancy or potentially leukemogenic therapy). In 86 patients (15.0% of all AML patients; 60.1% of all sAML patients), sAML transformed from myelodysplastic syndrome (postMDS-AML). Patients with MDS were followed or treated for different periods of time. 58 patients (10.0%; 39.9%) were followed or treated for various malignancies (incl. cMPN) or were treated with potentially leukemogenic agents because of non-malignant disorders (t-AML). One patient was treated for two AML forms – after treatment of primary AML, secondary AML was diagnosed – see the case report.

As for the causes or diseases preceding the development of AML, most cases were ascribed to chronic myeloproliferative disorders (11 patients – 7.7%) and breast cancer (10 patients – 7.0%). The complete review of the causes of sAML is shown in the table. Distribution of patients according to the pathogenesis of AML is depicted in Figure 1. As the complete information about drugs used in cytotoxic therapy was not available in many patients, the type of therapy is not listed.

The follow-up was significantly longer in the group of treated patients with primary AML than in those with secondary AML (median 58 vs. 32 weeks, p = 0.0002).

The comparison of all patients' ages (incl. untreated patients) showed that patients with sAML were significantly older

Table. A complete review of the causes of sAML (except MDS).

11 x myeloproliferative disorder (5x osteomyelofibrosis, 2x myeloproliferation Ph negative NS, 2x polycythemia vera, 2x essential thrombocytemia)
9 x breast cancer
4 x endometrial (uterine) cancer
4 x prostate cancer
3 x thyroid carcinoma
3 x seminoma
2 x colorectal cancer
1 x breast cancer + endometrial cancer
1 x colorectal cancer + cervical cancer + thyroid cancer
1 x ovarian cancer
1 x lung carcinoma + bladder carcinoma
1 x gastric carcinoma
1 x gastric sarcoma
1 x gastric neoplasia NS
1 x Grawitz tumor
1 x Grawitz tumor + melanoma
1 x osteosarcoma of the femoral bone
1 x AML with inv(16)
1 x B-cell acute lymphoblastic leukemia
1 x Hodgkin's lymphoma
1 x peripheral T-cell non-Hodgkin's lymphoma
1 x diffuse large B-cell lymphoma
1 x B-cell chronic lymphocytic leukemia
1 x mycosis fungoides
1 x systemic mastocytosis
1 x severe aplastic anemia
1x Down's syndrome
1 x actinotherapy of keloid scars
1 x long-term immunosuppression for systemic lupus erythematosus

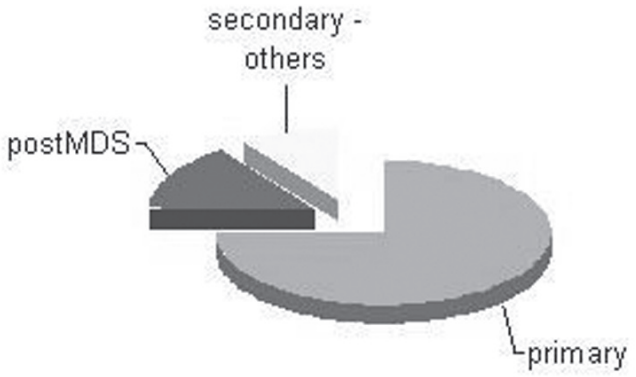

Figure 1. Distribution of patients according to pathogenesis of AML

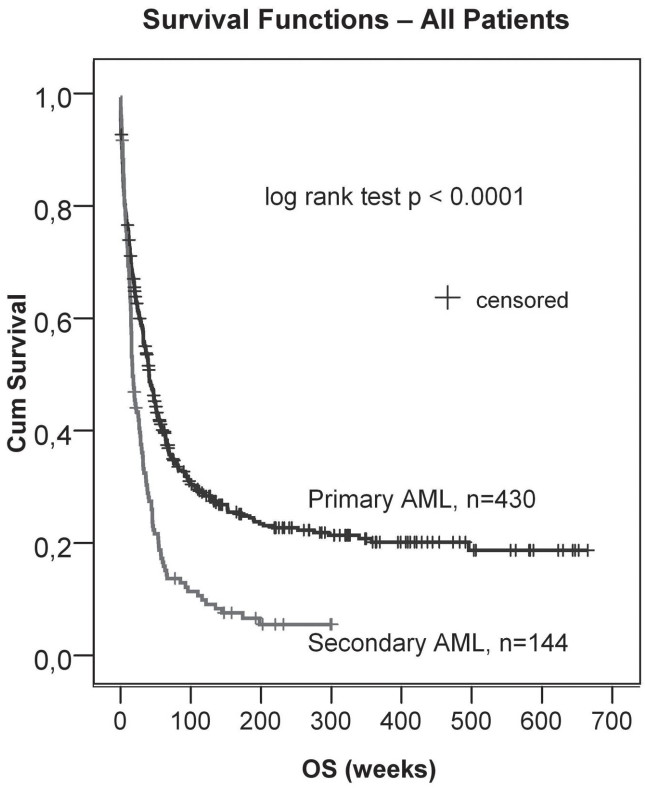

Figure 2. Overall survival curves of all patients – the comparison of primary and secondary AML

than those with primary AML – the median age 64 (20 – 87) vs. 58 (18 – 80) years (p = 0.0003), as expected.

The comparison of curative treatment in patients with secondary or primary AML yielded the following results: The two groups did not differ significantly – the median age 55 (20 – 76) vs. 53 (18 – 80) years (p = NS), sex (m:f; %) 45:55 vs. 49:51 (p = NS). Patients with sAML had significantly worse cytogenetic findings – there were significantly more patients with unfavorable cytogenetic prognosis (i.e. del (5), 5q-, del (7), 7q-, 11q23 rearrangement, complex karyotype) and fewer patients with favorable outlook (i.e. inv/t(16) and t(8;21); patients with acute promyelocytic leukemia are evaluated separately in this article) (p = 0.0003). The group of secondary AML patients comprised 4 patients (5.8%) with acute promyelocytic leukemia (APL), 20 patients (29.0%) with intermediate cytogenetic prognosis (i.e. normal karyotype and cytogenetic changes other than favorable or unfavorable) and 33 patients (47.8%) with unfavorable prognosis; in 12 patients (17.4%), cytogenetic analysis was not performed or was unsuccessful (insufficient number of metaphases). Secondary AML patients had lower numbers of leukocytes at diagnosis – the median was 3.8 x 10^9/l (0.9 – 350) in sAML vs. 12.6 x 10^9/l (0.5 – 411.3) in primary AML (p = 0.001). The subgroup of treated sAML patients did not differ from the group of all sAML patients – in 38 (55.1%) patients, sAML originated from MDS. The median age did not differ between the subgroup (postMDS-AML) and the other sAML: 56 (26 – 76) vs. 53 (20 – 72) years (p = NS). With the exception of APL patients, there was not significant difference between these subgroups according to cytogenetic prognostic groups: postMDS-AML: 34.2% intermediate prognosis, 44.7% unfavorable prognosis, 21.1% were not examined or the examination was not successful; other sAML: 4 (12.9%) with APL, 6 (19.4%) intermediate prognosis, 17 (54.8%) unfavorable prognosis, 4 (12.9%) were not examined or the examination was not successful. There was also no difference in the number of leukocytes at diagnosis in both subgroups: 3.7 x 10^9/l (1.1 – 350) vs. 4.0 x 10^9/l (0.9 – 174.4) (p = NS).

Curative chemotherapy was indicated in 69 patients (47.9%) out of 144 patients with sAML. The proportion of treated patients in this group was significantly lower than in the group with primary AML – 305 out of 430 patients (70.7%) were treated with curative chemotherapy (p < 0.0001).

As for treatment responses, 46.4% of patients with sAML achieved complete remission (CR); 73.0% with primary AML (p < 0.0001). A total of 62.5% of patients with sAML relapsed, the median duration of CR in relapsing patients was 29 (14 – 140) weeks. Only 2 patients (6.9%) responded to subsequent treatment, but second CR was short, only 19 weeks in one of them. The other one has only been in CR for a short time and has undergone allogeneic stem cell transplantation recently. A disease-free survival of more than 1 year was achieved in 15.9% of patients.

A total of 47.6% of patients with primary AML relapsed in the median of 39 (12 – 279) weeks after reaching first CR. There was no statistically significant difference when compared with the sAML group. Second CR was achieved in 37.4% of patients with primary AML (p = 0.016). A disease-free survival of more than 1 year was achieved in a significantly higher proportion of patients – 42% (p < 0.0001). Overall survival (OS) curves using the Kaplan-Meier method in all patients and in curatively treated patients are shown in Figures 2, 3 and 4. Event-free survival curves of primary and secondary AML

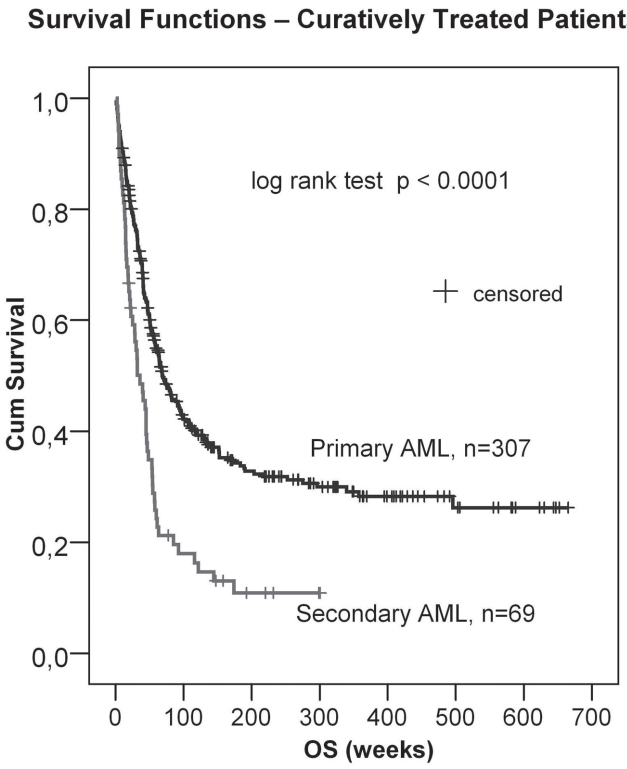

Figure 3. Overall survival curves of curatively treated patients – the comparison of primary and secondary AML

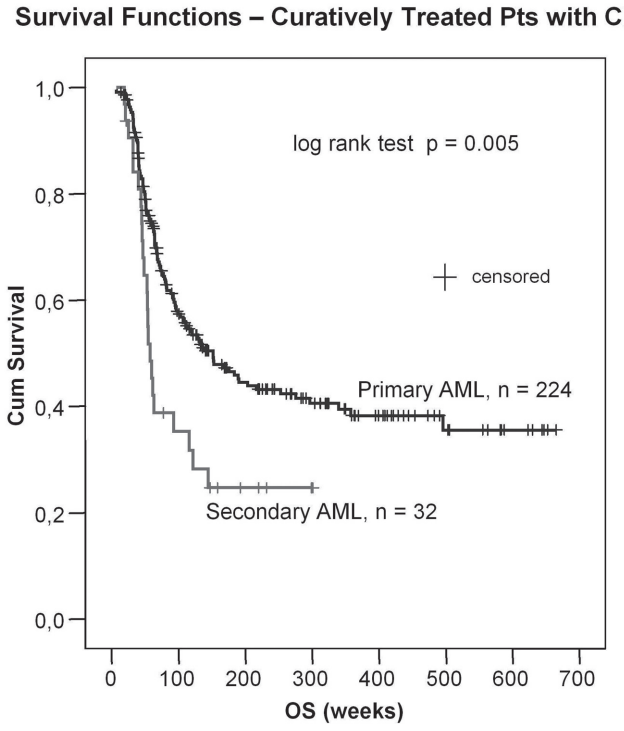

Figure 4. Overall survival curves of curatively treated patients with complete remission – the comparison of primary and secondary AML

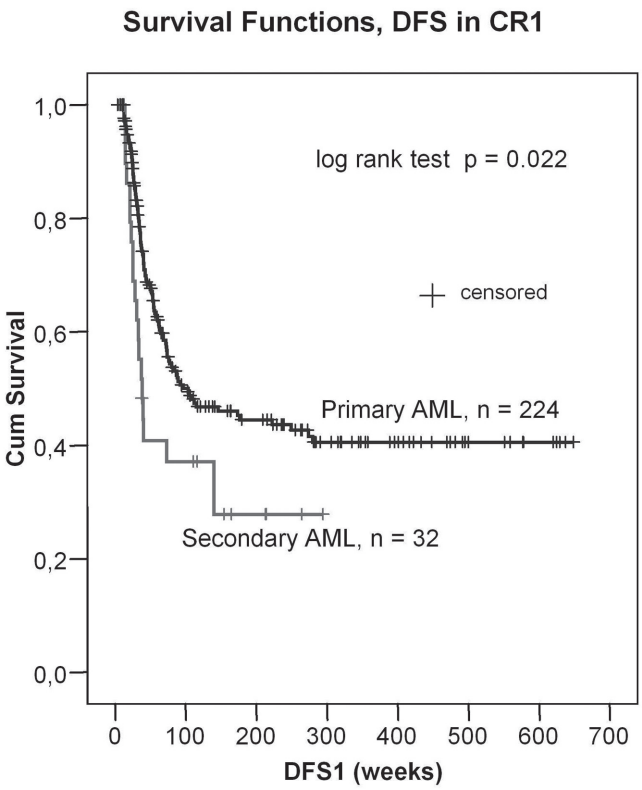

Figure 5. Disease-free survival curves of curatively treated patients since the first complete remission achievement – the comparison of primary and secondary AML

patients after reaching first CR are depicted in Figure 5. Overall survival curves comparing postMDS-AML and other sAML are plotted in Figure 6.

The comparison of results in different cytogenetic prognostic subgroups of treated patients shows the following:

a) APL - 4 patients in our group had secondary acute promyelocytic leukemia (sAPL). One patient with peripheral T-NHL was treated at our department long time ago. Three patients were treated for different types of carcinoma: papillary adenocarcinoma of the thyroid gland (4 doses of radioactive iodine), cervical cancer (actinotherapy) and breast cancer (actinotherapy). All patients achieved complete molecular remission of the disease after combined chemotherapy with all-trans retinoic acid. Molecular relapse of sAPL was observed in patients with M3v variant, leukocytosis at diagnosis (i.e. high-risk disease, Sanz). Second molecular remission was achieved after administration of arsenic trioxide.
b) Favorable prognosis (with the exception of APL): AML1/ETO or CFBβ/MYH11 leukemia was not recorded.
c) Intermediate prognosis: n = 20; 40% CR, 62.5% first relapse, 30% of patients DFS > 1 year.

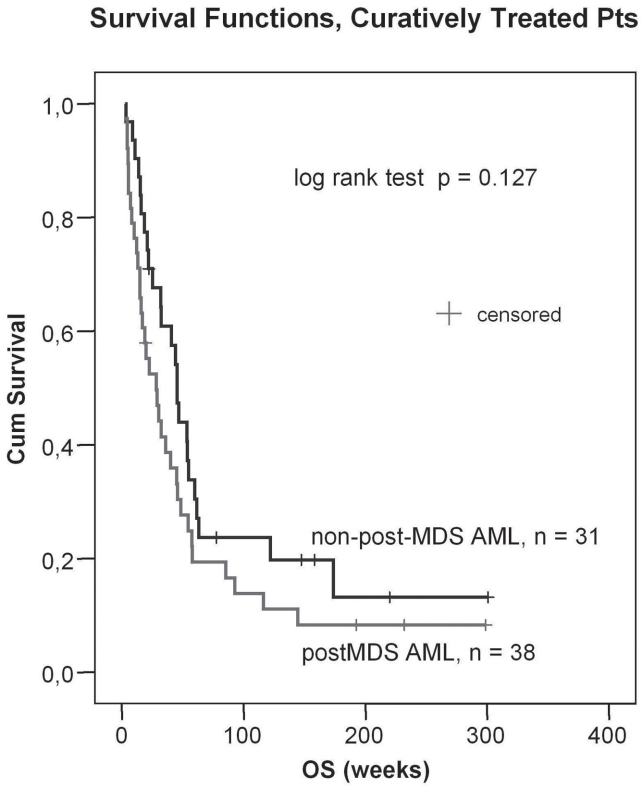

Figure 6. Overall survival curves of curatively treated patients with secondary AML – the comparison of postMDS-AML and the others

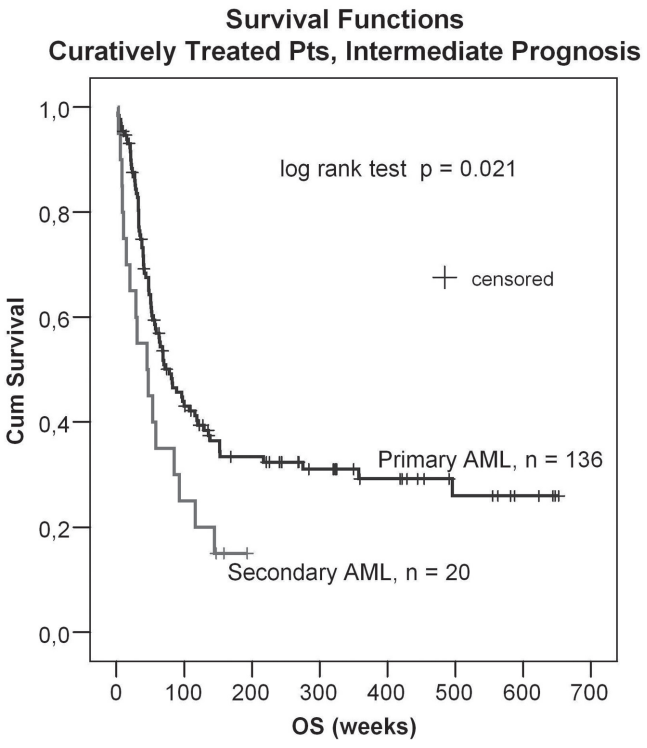

Figure 7. Overall survival curves of curatively treated patients with intermediate cytogenetic prognosis – the comparison of primary and secondary AML

Primary: n = 136; 82.4% CR (p = 0.0002), 49.1% first relapse (p = NS), 44.1% DFS > 1 year (p = NS). Survival curves using the Kaplan-Meier method are shown in Figure 7.

d) Unfavorable prognosis: n = 33; 36.4% CR, 66.7% first relapse, 6.1% DFS > 1 year.
Primary: n = 89; 51.7% CR (p = NS), 60.9% first relapse (p = NS), 23.6% DFS > 1 year (p = 0.028). Survival curves using the Kaplan-Meier method show significant differences between primary and secondary AML in this cytogenetic subgroup (Figure 8).

The probability of achieving complete remission is significantly higher in primary AML with intermediate cytogenetic prognosis. Significantly higher proportion of primary AML patients with unfavorable cytogenetic prognosis achieved a disease-free survival of more than 1 year. The other differences with better results in prognostic subgroups of primary AML were not statistically significant, probably due to the low number of patients. The curves show worse OS not only in the above-mentioned subgroups according to cytogenetic risk, but also according to age (under 60 and over 60 years – Figures 9 and 10) and also in 2 of 3 subgroups according to the number of leukocytes at diagnosis (Figures 11, 12 and 13).

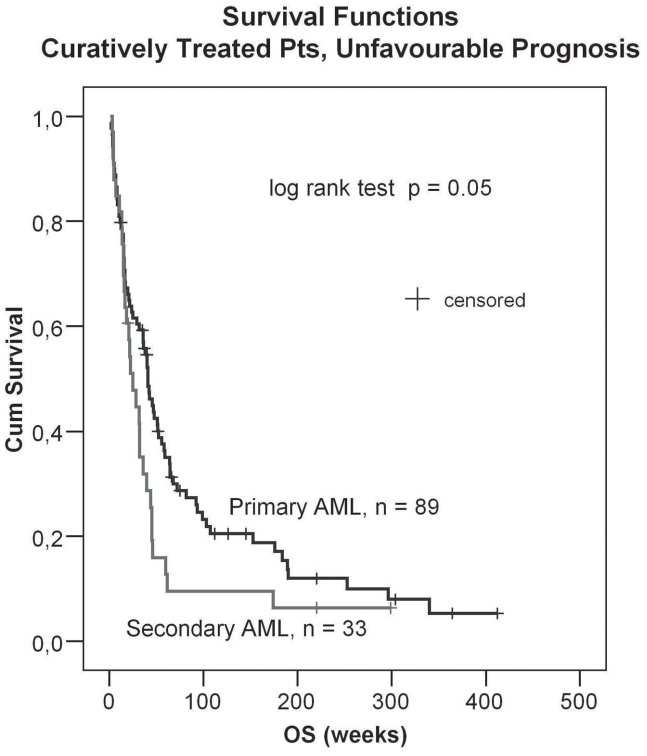

Figure 8. Overall survival curves of curatively treated patients with unfavorable cytogenetic prognosis – the comparison of primary and secondary AML

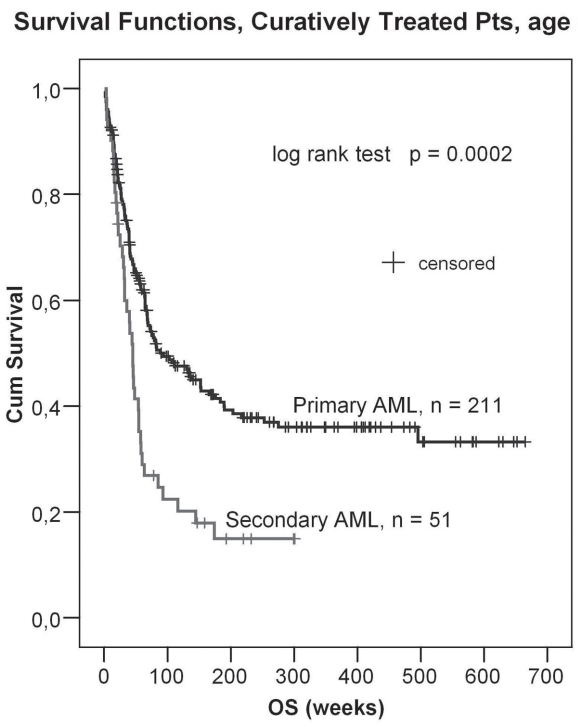

Figure 9. Overall survival curves of curatively treated patients under 60 years of age – the comparison of primary and secondary AML

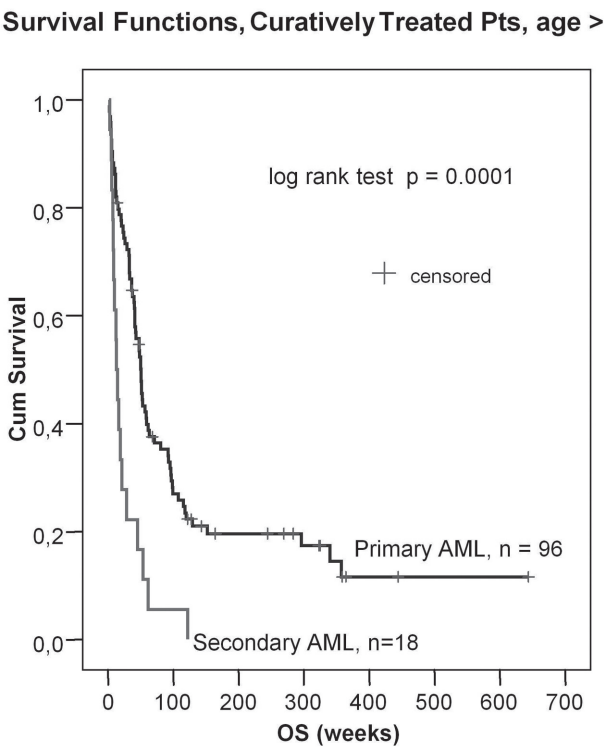

Figure 10. Overall survival curves of curatively treated patients over 60 years of age – the comparison of primary and secondary AML

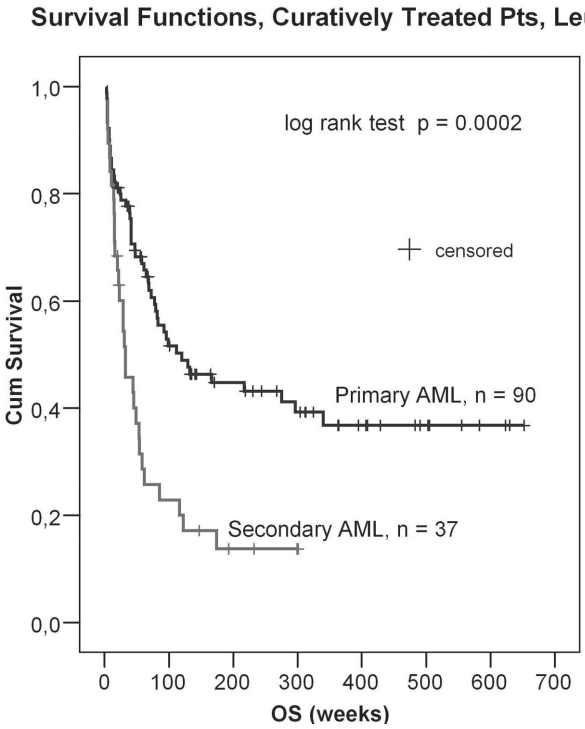

Figure 11. Overall survival curves of curatively treated patients with leukopenia at diagnosis – the comparison of primary and secondary AML

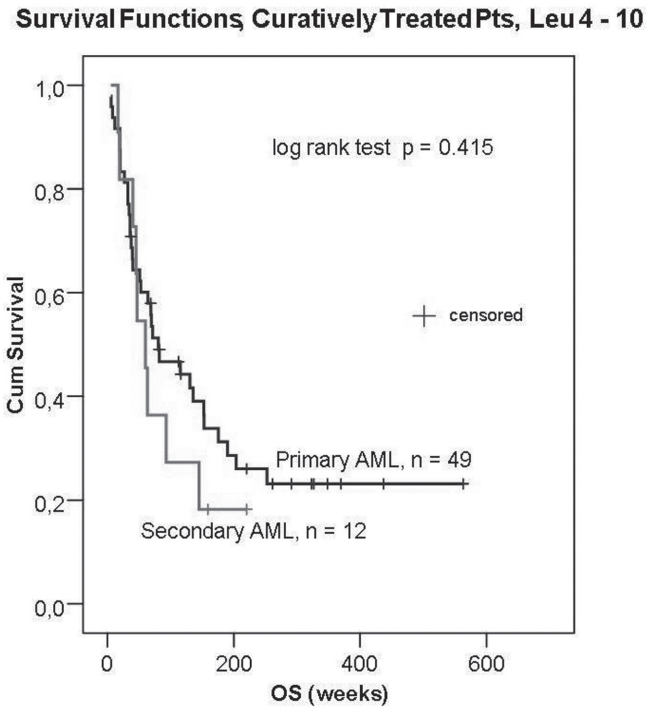

Figure 12. Overall survival curves of curatively treated patients with normal leukocyte count at diagnosis – the comparison of primary and secondary AML

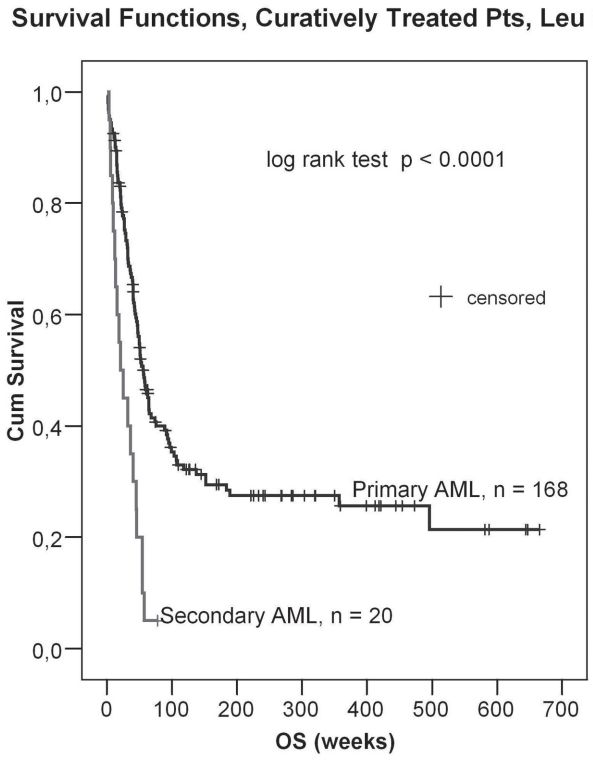

Figure 13. Overall survival curves of curatively treated patients with leukocytosis at diagnosis – the comparison of primary and secondary AML

Five patients with t-AML (3 with sAPL, 1 after alloHSCT and the patient mentioned in the case report) and 3 patients with postMDS-AML (all of them after alloHSCT, allografted not in CR) have survived in the long term. One patient with postMDS-AML is supposed to be allografted.

Hematopoietic stem cell transplantation in patients with secondary AML. Thirteen patients (18.8%) were transplanted (with peripheral blood stem cells) - 2 autologous and 11 allogeneic transplants. The autologous transplants were performed in first CR of sAML. The allogeneic transplants were usually performed in first CR (5 patients) or in first partial remission (PR, 1 patient). In 2 patients (MDS progression to AML) alloHSCT was the primary therapy and 2 patients were allografted in the phase of primary resistant active disease. In 1 patient, chemoresistant-relapsed disease was described. Eight patients were transplanted from HLA-identical siblings, three from unrelated donors.

Complete remission after transplantation was achieved in 5 out of 6 patients (alloHSCT was not performed in CR). Four patients (2 allografted in the active phase of primary resistant disease, 1 in PR and 1 in CR) have survived for long term. The median OS is 212 (158 – 299) weeks. The cause-specific mortality was as follows: relapse and progression of AML (5x), transplant complications (2x), infection (1x) and relapse and progression of primary malignancy – lung cancer (1x).

Special attention should be paid to the case report of a patient with severe aplastic anemia (SAA) who was treated with corticosteroid- and cyclosporine A-based immunosuppressive therapy combined with filgrastim and molgramostim. AML developed in the period of AA remission. Blasts contained MLL gene rearrangement (11q23). There was early relapse of the disease - after achieving complete remission - which was chemoresistant.

A 20-year-old patient with Down's syndrome was having her therapy considerably reduced and modified with regard to mental impairment. Complete remission was achieved but only for a short time.

Generally, as of December 31, 2008, 9 out of 69 (13.0%) treated patients were surviving in complete remission with sAML, the median age was 48 years and median follow-up 193 weeks (20 – 301). Four patients were allografted, three had acute promyelocytic leukemia, 1 patient achieved CR short time previously (alloHSCT was planned) and 1 patient was not allografted (see the case report).

Twelve patients did not experience relapse. Aside from the 8 surviving patients (1 above-mentioned patient had been in second CR for a short time) – 2 patients died in AML remission (relapse or progression of primary malignancy – T-NHL, lung cancer) and the remaining 3 patients died due to complications of AML treatment.

Case report. An unusual case of primary AML with inv(16) in a 53-year-old patient treated since July 2003 is presented here. After the standard induction (cytosine arabinoside + mitoxantrone + etoposide), complete remission was achieved. Three cycles of consolidation chemotherapy with intermediate-dose cytosine arabinoside were administrated. Complete remission was verified repeatedly. In October 2004, blast cells (48%) were identified during routine bone marrow examination. However, cytogenetic and molecular biology analyses showed durable molecular remission of inv(16) AML. But some new cytogenetic aberrations were identified – MLL gene rearrangement in band 11q23 in the form of t(11;18) dominated (FISH). This secondary AML probably resulted from the effects of topoisomerase II inhibitor administration (etoposide, mitoxantrone) in primary chemotherapy. Complete remission was achieved after FLAG (fludarabine + cytosine arabinoside + filgrastim) chemotherapy. Two cycles of intermediate-dose consolidation chemotherapy were administrated (complicated by severe infections). The infections and no sibling donor available contraindicated alloHSCT, although the prognosis was unfavorable. The standard consolidation chemotherapy could not be administered and low-dose cytosine arabinoside was used for treatment in an outpatient clinic. Eleven cycles were administered, the last in July 2008. She is in complete hematologic and cytogenetic remission of both AML types. The course of the described AML and the treatment result are rather atypical with regard to the expected course of the disease, literature data and the secondary role of AML with the presence of unfavorable cytogenetic abnormalities (12).

Discussion

Secondary AML accounts for 10 – 30% of all AML. The majority of patients progress from MDS to AML (60 – 70% of all sAML cases) (13). In this regard, our data were no different. Secondary AML was classified in 25 % of our patients and postMDS leukemia accounted for the major part (60.1 %) as we had expected.

As far as the age is concerned, sAML is more frequent in older patients. It is probably associated with a higher incidence of MDS and other malignancies in the older population. [4]. Statistically significant differences in age are not observed in the group of curatively treated patients due to their selection for this type of therapy. Secondary AML is an unfavorable prognostic marker in patients under 60 and over 60 years of age (Figures 9 and 10).

The leukocyte count at diagnosis was significantly lower in sAML; there is no significant difference between post-MDS-AML and other sAML. The prognostic significance of leukocytosis remains ambiguous (with the exception of hyperleukocytosis of over 100 x 10^9/l) [14]. The results of various studies (focused on initial leukocyte count and its prognostic significance) are not uniform. There is no clear explanation for significantly lower leukocyte count in sAML patients at diagnosis. The overall survival curves (based on initial leukocyte count) provide some interesting information (Figures 11, 12 and 13). The overall survival is significantly better in primary AML patients with leukopenia or leukocytosis, whereas there is no observed significant difference between primary and secondary AML patients with normal leukocyte count. However, this can be influenced by low numbers of patients.

As for cytogenetic findings, there are significant differences in the proportion of particular prognostic subgroups. In sAML, the favorable subgroup (statistically non-significant also intermediate subgroup) constitutes a minor proportion; on the contrary, the unfavorable group constitutes a major proportion. This is not surprising as unfavorable cytogenetic findings in sAML patients are associated with worse prognosis. The chances of achieving CR are significantly lower if the therapy results of primary and secondary AML (intermediate risk) are compared in basic parameters. Also the risk of relapse is higher and the long-term survival is lower - statistically non-significant. This shows that secondary origin of AML is an independent unfavorable prognostic factor.

We could not perform a valid statistical comparison in patients with acute promyelocytic leukemia (small number – 4 – of patients with secondary form; 36 patients with primary APL, 91.7% CR, 12.1% relapse). However, the therapy results indicate no difference in the prognosis of primary and secondary APL with efficient therapy. Literary data show similar results (15). Secondary AML1/ETO or CBFβ/MYH11 - leukemia was not recorded.

Allogeneic stem cell transplantation is considered to be the most effective therapy for sAML, but it cannot be used in all cases due to patients' status and comorbidities. In our group, eleven patients in different phases of the disease were allografted. Even though the number of allografted patients is small and the results cannot be statistically evaluated, some conclusions can be drawn. AlloHSCT is a curative method in sAML, even if not performed in CR. Six patients were transplanted not in CR, three out of them survived long-term. However, only one patient allografted in CR achieved the same outcome. When compared with primary AML, out of ten patients allografted not in CR, only one survived (allografted without active disease - bone marrow aplasia after salvage therapy administered in disease relapse). Interestingly, three of long-term surviving patients were postMDS-AML – these patients were not in CR at the time of alloHSCT. We can speculatively attribute this to the small number of patients ("the law of small numbers") or different kinetics of postMDS-AML (similar to leukocyte count at diagnosis as mentioned earlier).

A higher risk of AML as well as acute lymphoblastic leukemia (ALL) is observed in Down's syndrome. Megakaryoblastic AML (AML M7, FAB classification) dominates in these patients (80% of all AML). They usually have a favorable prognosis (16). AML was classified as M1 (FAB) in our patient with Down's syndrome. Only short-term complete remission was achieved with reduced and modified chemotherapy.

In conclusion, the prognosis of patients with sAML who are not allografted is unfavorable. Patients with sAML are older and curative treatment is less frequent than in primary AML. Their prognosis is worse according to cytogenetic analysis. The probability of achieving complete remission is lower, relapse is more frequent and overall survival is worse in almost all prognostic subgroups. With some exceptions, secondary AML (with the exception of secondary APL, the prognosis of which does not differ from favorable prognosis of primary AML) cannot be conventionally cured.

It can be supposed that the incidence of secondary AML will grow in proportion to the ageing population and higher numbers of successfully treated patients with malignancies. This should be considered especially when treating young patients.

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