DISCUSSION

Acute myeloid leukemia (AML) is characterized by a clonal proliferation of myeloid precursors with reduced capacity to differentiate into more mature cellular elements. [163]

The response to treatment and overall survival of patients with AML is heterogeneous. A number of prognostic factors related to patient and tumor characteristics have been described for AML, including age, performance status, and karyotype. [164]

There are several clinical findings that may help predict the likelihood of attaining a complete remission and subsequent disease-free survival in patients with AML. The strongest adverse clinical predictors are: advanced age, poor performance status, cytogenetic and/or molecular genetic findings in tumor cells, history of exposure to cytotoxic agents or radiation therapy and history of prior myelodysplasia or other hematologic neoplasms. [163]

Prognostic factors are urgently needed in order to be able to better predict treatment outcomes in defined subgroups of patients. Cytogenetic aberrations are among the most important independent prognostic factors. However, about two thirds of AML patients display a normal karyotype. This group has intermediate disease-free and overall survival, but the clinical outcome of individual patients within this group is still highly variable. Therefore, identification of parameters that allow the good risk patients to be separated from the bad risk ones within this cytogenetically defined group is crucial in order to improve risk-adapted treatment strategies in AML. [165]

A prognostic value of telomere shortening and telomerase activity has been suggested in various human hematopoietic malignancies, and some studies have investigated telomerase activity and telomere length in mononuclear cells from patients with AML. [166-168]

In the present study, telomere length and human telomerase reverse transcriptase (hTERT) level were measured in acute myeloid leukemia to detect if these parameters might be useful in providing insight into the clinical outcome of AML patients. The results of these markers were evaluated in relation to each other and in relation to different outcome.

The current study was performed on fifty consecutive AML patients. 36 patients (72 %) were younger than 60 years while 14 patients (28 %) were elderly (60 years or older). AML patients were subclassified according to the French-American-British (FAB) classification system, 31 (62 %) cases were M2, 9 (18 %) cases were M1, 6 (12 %) cases were M4 and other types (M3,M5,M6,M7) represented by only one case for each. This is in accord to what has been reported in literature that the common FAB types M2 and M1.[168]

Karyotype analysis with metaphase cytogenetics is a key component of the initial evaluation of a patient with AML; specific cytogenetic abnormalities in AML have considerable prognostic significance and affect treatment planning. [169]

Conventional cytogenetic was done for 18 patients only. Normal karyotyping were found in thirteen patients, three patients had monosomy 7, one patient had trisomy 21, and one patient had t (15, 17). So, 59 % of AML patients had normal karyotype pattern. Chromosome abnormalities were detected in 40% of patients, near percentage were detected by Meng et al in 2013. [170]

Median age of our patients was 55 years. Male to female ration was 1: 1.1. Although in adults, the median age of patient at diagnosis is approximately 65 years and male: female ratio is approximately 5:3 according to Siegal (2012) [171]; our results could be justified by the relatively smaller sample size.

Patients with AML generally present with symptoms related to complications of pancytopenia (eg, anemia, neutropenia, and thrombocytopenia), including weakness and easy fatigability, infections of variable severity, and/or hemorrhagic findings such as gingival bleeding, ecchymoses, epistaxis, or menorrhagia. [172]

Combinations of these symptoms are common. General fatigue is present in the majority of patients and often precedes the diagnosis for a number of months. Pallor and weakness are common and attributed to the anemia. Bone pain is infrequent in adults with AML, although some individuals describe sternal discomfort or tenderness, occasionally with aching in the long bones. This may be especially severe in the lower extremities, due to expansion of the medullary cavity by the leukemic process. [172]

The main presenting symptoms of AML patients were fatigue (96%), followed by bone pain (84%), fever (52%), and bleeding (50%). We found no statistically significant difference between elderly and adult AML patients regarding the clinical presentation of the disease.

Analysis of the peripheral blood at presentation in our study reveals a normocytic, normochromic anemia that can vary in severity. Most patients have platelet counts below 100 x 10^9/L at diagnosis, the median leukocyte count at diagnosis is approximately 8 x 10^9/L. The vast majority of patients have circulating myeloblasts that can be detected on the peripheral smear. Flow cytometry of the peripheral blood or marrow aspirate can identify circulating myeloblasts in the majority of patients by characteristic patterns of surface antigen expression. The specific pattern differs among the AML subtypes, but the majority of cases express CD34, HLA-DR, CD117, CD13, and CD33.

The patients were treated according to the standard chemotherapy protocol for induction and they were followed up by bone marrow examination at day 28 to determine patient's response. We followed all patients during the duration of the study (30 months).

In the present study, human telomerase reverse transcriptase (hTERT) level and relative telomere length were measured in all AML patients at diagnosis and compared with control subjects. The results of these markers were evaluated in relation to each other and in relation to different treatment outcomes.

Telomeres are the termini of eukaryotic chromosomes. Human telomeres are constituted of a tandem repeat of six base pairs (TTAGGG), which are wrapped in a protein complex. Telomere sequences are lost in each round of cell replication. The

biogenesis of telomeres is regulated by a large number of proteins and an enzyme called telomerase. [173]

Telomerase is active in germ cells, adult stem cells, activated immune cells, and 90% of cancer cells. However, it is absent or expressed at low levels in most adult differentiated cells and resting immune cells. [173]

Human telomerase reverse transcriptase **(hTERT)** is one of the three major components of the gene encoding telomerase. This catalytic subunit is considered as the key regulator for the control of telomerase activity, thus hTERT expression levels appear to parallel to telomerase activity. Moreover, the other two components of the gene are expressed in low level in tumor cells, thus recent studies targeted the expression hTERT as a marker of telomerase activity and discussed the feasibility of its quantitative evaluation. [174, 175]

In most reported studies, polymerase chain reaction (PCR) was the most widely used technique for detection of hTERT mRNA expression in tumor tissue, using a highly sensitive PCR-based assay, telomeric repeat amplification protocol (TRAP). However, detection of telomerase activity using hTERT mRNA expression in cells and tissues is somewhat difficult, it requires fresh or frozen tissue and is significantly affected by delays in freezing the cells, and low levels may be undetectable using PCR. Moreover, the existence of alternative splice variants of hTERT could cause misleading interpretation of hTERT mRNA expression. [175]

However, most cited authors used different methodologies to determine telomerase expression, thus, a direct comparison of the results of various studies is not possible. Also telomerase expression in tissues could be detected by immunohistochemical technique as Hiyama et al in 2001 [176] found that immunohistochemistry using polyclonal anti-hTERT can detect hTERT protein at the cellular level in paraffin-embedded cell or core biopsy samples, in spite of the very low abundance hTERT protein in tissues. Poirka et al in 2011 used ELISA technique to measure hTERT expression in serum of breast cancer patients.[177]

Recently, commercial **Enzyme-linked immunosorbent assay** (ELISA) kits for measuring telomerase are available and hTERT antibodies pre-coated to plastic micro well and during incubation hTERT from recombinant calibrator and samples bind to the pre-coated antibody.

In the present study, ELISA technique was used for detection of hTERT expression, because it is simple, less expensive, does not need special equipment for detection and could be applied in routine daily work.

There have been a limited number of investigations evaluating the relation between hTERT and clinical outcome in hematological malignancies; the present study looks comprehensively into levels of serum hTERT in both normal and AML patients and to correlate levels of hTERT with different treatment outcome.

In the current study, **hTERT** was evaluated in all control subjects and AML cases. hTERT levels was significantly higher in AML cases than in control subjects. It is consistent with previous reports that hTERT level is increased in several solid tumors as in

lung cancer [178], colorectal cancer [179], breast carcinoma [180], laryngeal squamous cell carcinoma [181], in gynecological malignancies [182] and in hepatocellular carcinoma [183]. Also it is consistent with previous reports in hematologic neoplasia. [184-186] As most malignant tumors show hTERT activity so induction of hTERT expression results in telomerase activity and contributes, as part of a multistep process, to human carcinogenesis.

As opposed to the finding of elevated telomerase activity in the majority of AML patients [184, 186], we found, in line with other studies, that hTERT mRNA was expressed in only 21% of new diagnosed AML patients. [187] These observations are supported by a study of Xu *et al.* [188] who showed that hTERT expression was only detectable in AML samples with intermediate or high levels of telomerase activity, as detected by the TRAP assay. It has been proposed that alternative splicing of hTERT is involved in regulation of telomerase activity. [189] As cancer cells may maintain telomerase by one of two pathways, a classic pathway in which the telomere is elongated when hTERT, adds new nucleotides.[100] An alternative mechanism is used by some tumors in the absence of telomerase activity called, alternative telomere lengthening (ALT). [106]

However Hartmann et al in 2005 [184] supported our finding in their study as they analyzed its different splicing patterns in AML samples, and hTERT expression was correlated very well with the expression of the active hTERT splicing variant. So their data suggest that alternative splicing does not seem to be the crucial mechanism by which telomerase is regulated in AML patients.

In the present work, no statistically significant correlation was found between hTERT level and **patients' age.** Also no relation found between hTERT level and **sex and FAB subtypes.** There was no statistically significant difference between elderly and young adult AML patients as regards hTERT level.

In our study, we observed that hTERT level at diagnosis was significantly lower in patients who achieved complete haematological remission than patients who did not achieve complete haematological remission suggesting that hTERT level may act as a predictive marker for the outcome.

Engelhardt et al [168] revealed significantly increased telomerase in AML patients at diagnosis. Telomerase decreased after induction chemotherapy, which correlated with the disappearance of leukemic cells and with the attainment of remission and, conversely, whereby a substantial telomerase increase was observed with MDS progression to RAEB and AML.

In addition when we compared serum hTERT level between patients who survived till the end of the study (total duration of the study was 30 ms) and patients who died during the study either early or during follow up period, we found a highly statistical significant difference between both groups as regards mean hTERT level ($p = 0.001$). These observations also suggest that high hTERT level could be considered as poor prognostic factors.

Porika M et al in 2011 [177] found that the expression of serum hTERT was significantly positively correlated with telomerase activity in breast cancer tissues. Pretreatment serum hTERT levels showed a significant positive correlation with clinical

stage, while correlation with nodal status and tumor size were marginal and no correlation was found with family history and age. Therefore, serum hTERT could have a potential application as a novel biomarker for breast cancer diagnosis.

Also in the present study, telomere length was successfully determined by quantitative PCR in AML cases at diagnosis and in normal control subjects. Mean telomere length (T/S ratio) was 0.4 (range: 0.01–1.1) in AML cases. When compared with healthy control, telomere length in AML cases was significantly very short, confirming previous reports. [184, 190, 191] This might suggest that when telomere shortening either by replication-dependent or independent mechanisms becomes more pronounced and, as a consequence, telomerase upregulation becomes essential to prevent replicative senescence of the malignant clone.

No statistically significant correlation was found between RTL (T/S ratio) and **patients' age.** Also no relation found between RTL level and **sex and FAB subtypes.** These results are consistent with the study of Aalbers et al in 2013 [191] on pediatric AML, who found that telomere length in leukemic cells was not associated with age, sex and FAB subtypes.

When we compared telomere length of AML patients in adult and elderly patients, patients younger than 60 years had longer telomere length than did patients older than 60 years but the difference in telomere length was not statistically significant. This finding is expected as telomeres within hematopoietic cells and other somatic tissues progressively shorten with age. Hartmann et al in 2005 [184] found significantly shorter telomere length in the younger group of patients; this could be attributed to a higher proportion of karyotypic abnormalities in the younger patients than in the older patients in their population of patients most likely contributed to these results.

Within the FAB classification subtypes, patients with the monocytic subtype (M4 and M5) had shorter telomere length than AML of less mature granulocytic origin (M1, M2). The same results were reported by Hartmann et al [184] as they reported that the degree of telomere shortening varies in AML according to FAB subtype, with the more differentiated subtypes showing increased shortening. This could be explained by increased proliferation rate in monocytic subtypes, Hartmann et al found that, there was an increased fraction of FLT3-activating mutations in patients with AML FAB M5,which could account for an increased proliferation rate.

Additionally, a significant negative correlation was found between hTERT level and relative telomere length in the present study. Our result is in line with previous report by Tukun et al in 2006 [193]. The specific role of telomerase in tumorigenic transformation is provision of an unlimited dividing capacity. Furthermore, telomerase reactivation is a requirement -if not cause- for unlimited proliferation, which is an essential characteristic of cancer cells. This unlimited dividing capacity provided by telomerase leads to progressive telomere shortening. Also as we mentioned above telomere shortening induce telomerase up regulation.

In our study, relative telomeres length were longer in patients who achieved remission than in patients who did not achieve remission but the difference in mean relative telomere length was not statistically significant, may further study with large

sampled could help to verify its significance. This is in agreement with previous results reported by Engelhardt et al in 2000 [168].

Also Engelhardt et al reported that in AML and MDS patients, longer telomeres were found after induction chemotherapy, most likely due to the loss of the leukemic clone (with shorter telomeres) and the emergence of normal hematopoietic cells (with longer telomeres). [168]

In the current study, median RTL was compared between cases who died during induction period and patients who survived. RTL was shorter in cases who died than in survived cases after induction therapy, (RTL was 0.2 and 0.5 respectively). The difference in length was borderline statistically significant ($p = 0.057$).

Similar results were reported by Boultwood et al in CML patients as there was a negative correlation between telomere length in the diagnostic period and duration to accelerated phase. [192] The above mentioned facts suggest that telomere length can be regarded as a prognostic factor in patients with haematological malignancies.

In addition when we compared relative telomere length between patients who survived till the end of the study (total duration of the study was 30 ms) and patients who died during the study either early or during follow up period, we found a highly statistical significant difference between both groups as regards mean RTL ($p = 0.001$). These observations also suggest that short telomere could be considered as poor prognostic factors.

Boultwood et al reported that in patients with chronic myelogeneous leukemia in late chronic phase, genetic instability due to progressive telomere shortening could be linked to up-regulation of telomerase activity and disease evolution in AML. [192] However, it remains unclear whether telomere length as a single parameter may be of prognostic relevance in AML. As shown by Hartmann et al [184] other parameters, such as FLT3 mutations, influence telomere length.

In a trial to elucidate the value of hTERT level as a predictive marker for outcome in AML, ROC curve was used in this study. The cut-off value of 57.57 ng/ml was used to separate AML patients into responders and non responders. A value below or equal to 57.57 ng/ml is considered to be a good predictive value, while higher values are worse predictive values. A value of 57.57 is of high sensitivity 69 % and specificity 56% for CR.

Porika M et al in 2011 [177] investigated the diagnostic implications of hTERT in the serum of breast cancer patients. The sensitivity and specificity of hTERT in cancer diagnosis was 68.9 and 83.3%, respectively, which is significantly higher than conventional markers.

Also ROC curve showed that certain RTL value (0.5) would be considered as a prognostic factor that could predict response in AML patients. (AUC) = 0.556, represents the overall accuracy of this value in predicting good response (complete haematological remission). This means that, in AML patients with value equal or more than 0.5, 55.6% of patients will achieve complete remission. **Sensitivity** of RTL cut-off value (0.5) as a predictive value for response was **50** %, and **specificity** was **56 %**. According to our

knowledge, no large studies assayed a cut-off value for RTL to compare our results with them.

We followed our patients during the duration of the study (30 ms) and Kaplan-Meier estimate was used to measure the fraction of subjects living for a certain amount of time after induction therapy. Also it was calculated for two groups of subjects. We found no statistical significant difference between young adult and elderly AML patients in mean survival time.

On the other hand, we found a high statistically significant difference in median survival time in patients who achieved remission and those who did not achieve remission (26 months and 4 months respectively). The same was observed in relapsed and non relapsed patients as there was a statistically high significant difference in median survival time (20 months and 26 months respectively).

When we studied survival according to the cut-off value of both hTERT and relative telomere length we found a statistically significant difference between patients with higher and lower value, with longer survival in patients with lower hTERT level and longer telomere length. These observations support the predictive role of hTERT in AML patients; also it could be used for follow up of chemotherapy.

Some studies have reported telomerase expression in acute and chronic leukemia [166-168]; however, up to our knowledge no large studies have assayed telomerase in quantitative manner. Furthermore, the relationship between telomerase and clinical outcome has not been adequately tested in AML. This information is necessary to understand the prognostic role of telomerase and to predict the efficacy of antitelomerase drugs currently in development. [194]

Targeting the hTERT catalytic subunit as anticancer therapy is theoretically tumor-specific and might be less toxic due to its specific expression in tumor and highly proliferating cells compared to other normal cells. Various newly discovered agents represent interesting anti-hTERT candidates for clinical drug development. [195, 196].

Telomerase inhibition was discussed as a promising approach for treating a variety of malignant tumours. The main prerequisites that should match if a tumour is suitable for telomerase-inhibition therapy: (i) Telomerase activity must be detectable and must therefore be the main mechanism of telomere maintenance. (ii) Telomerase activity must be significantly higher than those of normal tissue, especially of stem cells. In this case, inhibition of telomerase activity would shorten tumour telomeres faster to a critical length than in normal tissue and would therefore induce cell death selectively in tumour cells [197].

Improvement of survival due to advances in supportive care, chemotherapy regimens, and transplantation techniques has been observed in AML patients. [36] However, elderly AML patients show poor prognosis because of characteristics associated with their age. Characteristics such as fragile medical condition leading to the restriction of active treatments, a higher incidence of treatment-related mortality, and a higher proportion of patients in the high-risk group, including those with high-risk cytogenetic or genetic profiles who may be refractory to treatment, were suggested as the causes of poor clinical outcomes in elderly AML patients. [199]

The shorter survival in elderly AML patients in our study supported by Dombret H et al and Pollyea D et al [199, 200]. In our study, the median survival of elderly AML patients was 8 months; while in adult AML patients it was 10 months. No statistically significant difference in median survival was found between both groups (p=0.259). This result was not comparable to those obtained in other studies; this could be explained by different treatment pattern used.

On the other hand, we found a statistically significant relation between age and clinical outcome as mean age in patients who achieved CR was 45 years while in patients who did not achieve CR it was 54 years, there was a statistically significant difference between the two groups as regards mean age (t= -2.592, p=0.013*). These results are in line with many reports supporting old age as poor prognostic factor. [199. 200]

In our study, response rate was 52 % of which 38 % was in CR and 14 % in partial response, patients with CR had longer survival than non-CR patients (26 months vs. 4 months, respectively, P = 0.0001). Hyeon et al in 2014[201] studied the clinical characteristics and treatment outcome of acute myeloid leukemia in elderly patients, CR was 58 %. These results imply that a considerable length of survival can be expected in AML patients when they attain CR with intensive treatment.

The telomere and telomerase interactions appear to be an essential determinant for proliferative capacities of tumor cells. It has been known that telomerase activity provides the ability of proliferation to the malignant cell; thus, targeting of tumor cells by inhibiting telomerase may be an effective therapy. In the future multi-parameter assays, such as gene profiling, might be broadly applicable and might give light on the multiple pathways influencing pathogenesis and prognosis in AML.

SUMMARY

Acute myeloid leukemia (AML) refers to a group of hematopoietic neoplasms characterized by a clonal proliferation of myeloid precursors with reduced capacity to differentiate into more mature cellular elements. The response to treatment and overall survival of patients with AML is heterogeneous.

Prognostic factors are urgently needed in order to be able to better predict treatment outcomes. Cytogenetic aberrations are among the most important independent prognostic factors. However, about two thirds of AML patients display a normal karyotype. This group has intermediate disease-free and overall survival, but the clinical outcome of individual patients within this group is still highly variable. Therefore, identification of parameters that allow the good risk patients to be separated from the bad risk ones within this cytogenetically defined group is crucial in order to improve risk-adapted treatment strategies in AML.

The aim of the present work was to study telomere length and human telomerase reverse transcriptase (hTERT) level in acute myeloid leukemia and to detect if these parameters might be useful in providing insight into the clinical outcome of AML patients.

The study included 50 patients with acute myeloid leukemia and twenty healthy individuals with comparable age and sex. All subjects participating in this study were subjected to the following:

I- Thorough history taking.

II- Thorough clinical examination.

III- Routine work up:

- Renal function tests.
- Liver function tests.
- Radiological work up (chest X-ray, U/S abdomen &pelvis and ECHO)

IV- Diagnostic laboratory investigations

a- Complete blood picture (CBP).

b- Bone marrow examination.

c- Immunophenotyping.

V- Advanced investigations

a- Quantitative assessment of hTERT by ELISA.

b- A quantitative PCR method for measuring telomere length.

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The study included 36 patients with AML younger than sixty years, and 14 patients with AML sixty years or older. The age of AML patients ranged from twenty three to seventy one years with a mean age of 50.8±12.97. Twenty four (48%) patients were males and 26 (52%) were females. The most common clinical findings in our patients were fatigue (96%), followed by bone pain (84%), fever (52%), and bleeding (50%).

The hTERT levels in the control ranged from 2.04 ng/ml to 11.11 ng/ml. Mean level was 5.06 ± 2.32 ng/ml. serum levels in AML cases ranged from 4.9 ng/ml to 98 ng/ml. Mean level was 43.3± 25.4 ng/ml. There was statistically significant higher level of hTERT in patients than controls. Relative telomere length (RTL) in AML patients ranged from 0.01 to 1.1. Mean level was 0.4 ± 0.3. Mean telomere length in normal subjects was 3.75. There was statistically significant lower RTL in patients than control. There was a negative correlation between serum level of hTERT and the relative telomere length. No significant correlation was detected between RTL and hTERT and age, sex and FAB classification.

The patients were treated according to the standard chemotherapy protocol for induction and they were followed up by bone marrow examination. Nineteen cases achieved CR (complete response) after induction therapy, percentage of CR was higher in younger age group than in elderly. Fifteen cases died during first 28 days with higher percentage of deaths in the elderly. Seven cases attained partial response either in the form of no restoration of peripheral blood counts and/or bone marrow, percentage of partial response was higher in elderly. Nine cases achieved no response at all. Seven cases are younger than sixty and two cases are elderly, during follow up of cases nine cases who attained remission relapsed, seven cases are younger than sixty while 2 cases are elderly. Mean age was statistically significant lower in patients who achieved remission.

The median level of hTERT in cases that died during induction was 55.7 ng/ml while in survived cases it was 54.9 ng/ml. Median relative telomere length (RTL) was shorter in cases that died than in survived cases after induction therapy, (RTL was 0.2 and 0.5 respectively). Mean hTERT level in patients who did not achieve remission was statistically significant higher than that in patients who achieved remission. Mean RTL in patients who achieved remission was higher than that in patients who did not achieve remission (.56 and .37 respectively). At the end of the study (after 30 ms) we found that mean hTERT level was statistically significant higher in dead cases than mean level in censored cases (43.33 and 24.75 respectively). Mean RTL was statistically significant higher in censored cases than in dead cases (.725 and .341 respectively).

ROC curve showed that certain hTERT level (57.57 ng/ml) would be considered as a prognostic value that could predict response in AML patients. (Area under the curve (AUC) = 0.603, this means that, in AML patients with value less or equal to 57.57 ng/ml, 60.3% of patients will achieve complete remission. **Sensitivity** of hTERT cut-off value (57.57 ng/ml) as a predictive value for response was **69.2 %,** and **specificity** was **56 %.**

Also ROC curve showed that certain RTL value (0.5) would be considered as a prognostic value that could predict response in AML patients. (Area under the curve (AUC) = 0.556, this means that, in AML patients with value equal or more than 0.5, 55.6%

of patients will achieve complete remission. **Sensitivity** of RTL cut-off value (0.5) as a predictive value for response was **50** %, and **specificity** was **56 %**.

During duration of our study (30 months), number of events was 36 and censored cases were 14. Median survival time for all AML patients in the study was 10 months. Median survival time in elderly patients was shorter than that in younger patients. Median survival time in patients who achieved remission was statistically significant longer than that in those who did not achieve remission (26 ms, 4 ms respectively). Median survival time in relapsed patients was statistically significant shorter than that in non relapsed patients (20 ms, 26 ms respectively).

Median survival time in patients with hTERT level higher than cut-off level was shorter than median survival time in patients with lower value, (5 ms, and 14 ms respectively). There was a statistical significant difference in median survival time in both groups. Median survival time in patients with relative telomere length lower than cut-off value was shorter than median survival time in patients with higher value, (6 ms, and 14 ms respectively). There was a statistical significant difference in median survival time in both groups.

It was found that both relative telomere length and hTERT could be used for predicting treatment outcome in AML patients. This predictive impact of RTL and hTERT may be of help in assessing clinical behavior and outcome in AML patients. Targeting the hTERT catalytic subunit as anticancer therapy is theoretically tumor-specific and might be less toxic due to its specific expression in tumor and highly proliferating cells compared to other normal cells.

CONCLUSIONS

1- The response to treatment and overall survival of patients with Acute Myeloid Leukemia is heterogeneous; prognostic factors are urgently needed in order to be able to better predict treatment outcomes.

2- A prognostic value of telomere shortening and telomerase activity has been suggested in various human hematopoietic malignancies.

3- High telomerase activity and shorter telomeres are present in most studied cases; there is an inverse correlation between both.

4- The shortest telomere length were found in FAB subtypes M4 and M5.

5- Longer telomere length and lower telomerase level were found in patients who attained remission.

6- Survived cases had a longer telomere length and lower telomerase level than cases that died during our study.

7- Telomerase level below or equal to 57.57 ng/ml is considered to be a good predictive value, relative telomere length above o.5 is considered to be good predictive value.

8- Telomerase cut-off value is more sensitive than relative telomere length cut-off value.

9- Median survival was higher in patients with lower telomerase level than the cut-off value.

10- Patients with longer telomere length than the cut-off value had a higher median survival..

11- The telomere and telomerase interactions appear to be an essential determinant for proliferative capacities of tumor cells. It has been known that telomerase activity provides the ability of proliferation to the malignant cell; thus, targeting of tumor cells by inhibiting telomerase may be an effective therapy.