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Thyroid Function Following Treatment of Childhood Acute Lymphoblastic Leukemia

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1. Introduction

Acute lymphoblastic leukemia (ALL) is the most frequently encountered malignancy in childhood. Peak incidence is in early childhood. There is male predominance with 1.2:1 male to female ratio (Pui et al., 2006). Current therapeutic modalities have succeeded in assuring high cure rates. Treatment protocols involve mainly chemotherapy according to patient and leukemia risk classification. Irradiation therapy can be used as central nervous system (CNS) prophylaxis or as therapy for CNS involvement, although the use of CNS irradiation is reduced (Pui et al., 2009). Furthermore, allogeneic bone marrow transplantation can be used for very high risk patients or patients not responding to the treatment protocols (Pui et al., 2006).

Surveillance for long-term complications, following completion of chemotherapy is important, in order to prevent morbidity and to improve quality of life (Oeffinger et al., 2006). The vast majority of long-term sequelae are endocrine abnormalities involving the hypothalamic pituitary axis, the thyroid gland and the gonads. Growth hormone deficiency, precocious puberty, gonadal failure, hypothyroidism and thyroid cancer are the most likely long-term clinical presentations (Chemaitilly & Sklar, 2010).

The prevalence of hypothyroidism was found to be higher among childhood cancer survivors than in the general population, in a nation-wide registry of Finland. They reported the prevalence of hypothyroidism among cancer survivors, by reporting the clinically diagnosed hypothyroid patients who were receiving levothyroxine replacement therapy. Direct radiotherapy of the thyroid gland was related to a higher prevalence of hypothyroidism. Furthermore, they reported that females were more susceptible to hypothyroidism than males following childhood cancer (Madanat, 2008). Hypothyroidism, either primary or central, can be manifested in survivors of childhood malignancies (Madanat et al., 2007, Rose et al., 2006). The retrospective study by Madanat et al., reported that impaired thyroid function occurred in patients with a history of brain tumor, Hodgkin's disease, leukemia/non Hodgkin's lymphoma (NHL) and others. Age at diagnosis did not have an effect on the occurrence or time frame of development of thyroid hypofunction.

They found that radiotherapy combined with chemotherapy was associated with a higher risk for development of hypothyroidism, compared to chemotherapy alone (Madanat et al., 2007).

A recent report from the Japanese childhood cancer survivors program, reveals thyroid dysfunction in 18% of the patients, primary as well as central hypothyroidism. The vast majority of patients with primary hypothyroidism were irradiated to the neck area (Miyoshi et al., 2008).

Additional information derives from the registry of German patients, for the evaluation of side effects after radiation therapy in childhood and adolescence. The preliminary results of their report on the incidence of thyroid dysfunction come following a relatively short period of observation. The prevalence of thyroid dysfunction in patients treated for childhood ALL, is 11% which is much lower than the prevalence in patients treated for brain tumors. This is related to the lower dose of radiation given to the thyroid gland of ALL patients (Bőling et al., 2011).

Rose et al., reported on 62 patients with central hypothyroidism. Of those 10 patients (16%) had received chemotherapy only and none of these patients had hypothalamic tumors that would be clearly associated with endocrine dysfunction (Rose et al., 2006). Thus, they suggest that the occurrence of central hypothyroidism is more common than is thought, and they recommend a more vigilant and timely work-up in order to assure early identification and treatment of the hypothyroidism.

Thyroid dysfunction has been reported in survivors of childhood ALL in previous papers, but the incidence and the severity of thyroid dysfunction varies. ALL treatment protocols have evolved overtime, duration and intensity of the treatment, as well as medication combination and radiotherapy dose have changed. In a small group of Italian ALL patients, thyroid dysfunction was not appreciated during a 6 year follow-up period. However, a case of papillary thyroid cancer was identified (Neves Mascarenhas et al., 2006). In the paper published by Steffens et al, a retrospective analysis, primary hypothyroidism had occurred in patients treated for childhood ALL. The patients were divided in three groups, according to the therapeutic regime used: 1. chemotherapy only, 2. chemotherapy and cranial irradiation, and 3. combination of chemotherapy, cranial irradiation and bone marrow transplantation. Cases of hypothyroidism, as judged based on elevated serum TSH values were identified in all three groups but the higher incidence was appreciated in the latter group (Steffens M et al, 2008). Furthermore, there are reports of hypothyroidism in ALL patients, related to the use of craniospinal irradiation (Lando et al., 2001).

The papers presented, include pediatric patients diagnosed with ALL treated with different chemotherapeutic protocols with or without cranial irradiation and hemopoietic stem cell transplantation. The aim of the current retrospective study is to investigate a homogeneous group of children with ALL, treated with the same protocol (BFM). Patients with early death or relapse, as well as, patients who underwent hemopoietic stem cell transplantation in first remission were excluded from this analysis. Thyroid function was evaluated at diagnosis, at the end of chemotherapy, one to two years post chemotherapy completion and more than 3 years post treatment cessation. This study seeks to define the total prevalence of thyroid dysfunction in this homogeneously treated group of patients diagnosed with childhood acute lymphocytic leukemia.

2. Subjects and methods

The patient population included and analyzed retrospectively in this study, consists of the patient cohort with newly diagnosed acute lymphoblastic leukemia (ALL), treated according to the ALL-BFM protocols (ALL-BFM-90 and ALL-BFM-95 Protocols) from April 1994 to December 2010, in the Department of Pediatric Hematology-Oncology, at Agia Sofia Children's Hospital in Athens, Greece.

Acute lymphoblastic leukemia was diagnosed by bone marrow morphology and phenotype. Patients were assigned to the high risk (HR) treatment group if they had an absolute blast count on peripheral blood of more than 1.0 k/ul on day +8 of induction, following prednisolone treatment (prednisolone poor responders), no remission by bone marrow morphology on day +33 following induction or if they were found to have translocations t(4;11) or t(9;22) by karyotype or FISH at diagnosis bone marrow specimens. The rest of the patients were assigned to the median risk (MR) treatment group. Thus, standard risk (SR) patients were upgraded to the MR group (Schrapp et al., 2000, Moricke et al., 2008).

Figure 1 illustrates the outline of protocol ALL-BFM-90 and ALL-BFM 95 (Katsimpardi et al., 2006).

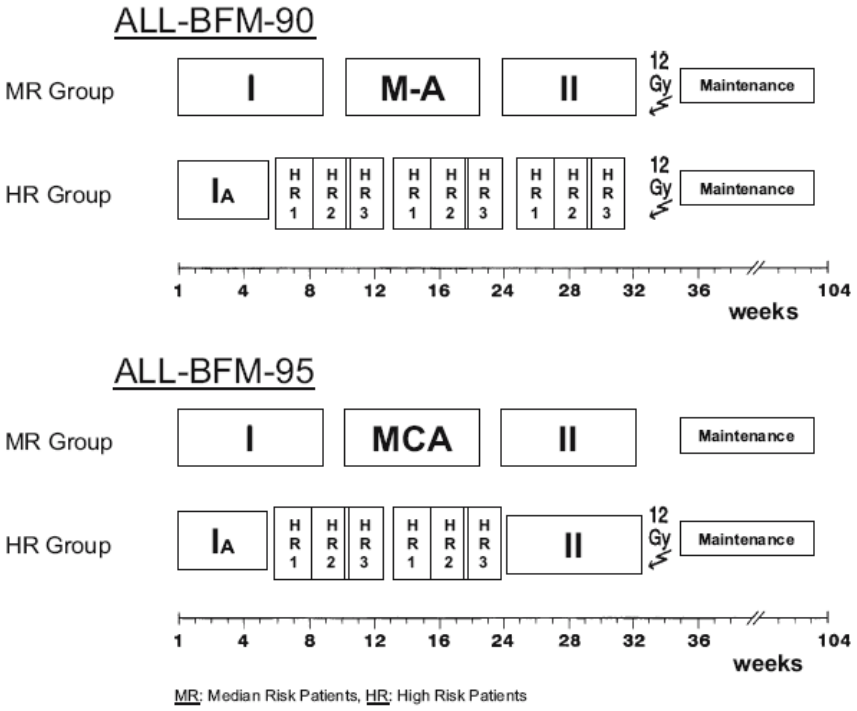


Fig. 1. ALL-BFM-95 and ALL-BFM-90 treatment protocol outline. From K Katsimpardi et al, Support Care Cancer (2006) 14: 277–284. DOI 10.1007/s00520-005-0884-6

Synopsis of the treatment schedule and strategy follows. Overall, treatment consisted of an induction, consolidation, reinduction and maintenance phase. The induction phase (Figure 1, Protocol I) was based initially on four drugs (prednisolone, vincristine, L-asparaginase and daunorubicin). Later (second phase of Protocol I, induction), two courses of 1 gr/m^2 of cyclophosphamide were administered at a 28-day interval, with 6-mercaptopurine p.o. and low dose aracytin i.v., for the interim time. This second part of the induction is omitted for all HR patients. The consolidation phase for MR patients (Figure 1, MA or MCA) was based on p.o. 6-mercaptopurine and 4 courses of high dose (5 gr/m^2) methotrexate i.v. The reinduction phase for the MR patients was similar to the induction phase (Figure 1, Protocol II), but with dexamethasone, vincristine, L-asparaginase and doxorubicin, initially. One dose of cyclophosphamide at 1 gr/m^2 with 14 days of 6-thioguanine and low dose i.v. aracytin followed (second phase of Protocol II).

Following only the initial phase of induction (Protocol IA), the high risk (HR) patient group received different, intensified treatment according to the protocol. Thus, patients treated according to the ALL-BFM-90 protocol received 9 blocks of treatment (in sequence: HR1, HR2, HR3 given in three series and no reinduction (ALL-BFM-90, Figure 1). Two of these HR blocks are based on high dose methotrexate (HR1, HR2) and one (HR3) is based on high dose aracytin. On the other hand, HR patients treated according to the ALL-BFM-95 protocol received 6 blocks of treatment (in sequence: HR1, HR2, HR3 given in two series). Then, reinduction with Protocol II followed, (ALL-BFM-95, Figure 1). Thus, Protocol II reinduction phase was common for MR and HR patients.

According to the protocols, all HR patients and all patients with T-precursor ALL received 12 Gy of cranial irradiation following the completion of the treatment that was described previously and prior to starting maintenance chemotherapy. MR patients were irradiated, as above, on the ALL-BFM-90 protocol but not on the ALL-BFM-95.

Allogeneic bone marrow transplantation (BMT) was recommended for a subset of HR patients, provided that a matched sibling donor was available.

Maintenance treatment consisted of 24 or 30 months in total for females and males respectively, of daily 6-mercaptopurine (50 mg/m^2) p.o./weekly methotrexate (20 mg/m^2) p.o. and monthly (28 day cycle) i.v. vincristine (1.5 mg/m^2), together with a five-day p.o. prednisolone (40 mg/m^2/day) pulse. Triple (methotrexate/ aracytin/ steroid, doses adjusted to age) intrathecal (IT) infusions every third pulse (84 days), were administered to patients not given CNS irradiation.

Overall, this ALL patient cohort has received more intensive treatment than the original ALL-BFM-90 and ALL-BFM 95 Protocol (Schrappe et al., 2000, Morriche et al., 2010). All SR group patients were treated according to the MR group (receiving additional 2 doses of anthracyclines) and maintenance treatment was increased in length (24 months for girls and 30 months for boys maintenance treatment in total) and was intensified with vincristine/ prednizolone monthly pulses and triple intrathecal infusions every third pulse. Detailed treatment schedule has been previously described. Details of the treatment schedule and patient outcome has been described before (Papadakis et al., 2003).

The purpose of this analysis is to evaluate the effect of ALL treatment on thyroidal function. Thus, in order to have a homogenously treated patient group, patients with early death or

relapse and patients who underwent bone marrow transplantation in first remission according to the Protocol were excluded from the analysis.

Two hundred twenty- three patients, were treated for newly diagnosed ALL according to the BFM Protocol (ALL-BFM-90 and ALL-BFM-95 Protocols) from April 1994 to December 2010. From them 18 have not yet completed the prescribed chemotherapy and 5 suffered early death from toxicity and thus they were excluded from analysis. Additionally, 32 patients were excluded from the analysis, of which 17 underwent stem cell transplantation in first remission and 15 patients due to early relapse. Thus, 168 patients were eligible for analysis and the sex distribution was 93 males and 75 females.

The median age at diagnosis was 5.1 years (range, 1.0 to 16.7 years). Median duration of treatment and median age at completion of maintenance treatment was 3.2 years (range, 2.1 to 4.2 years) and 8.2 years (range, 4.0 to 19.6 years) respectively. A total of 26 patients received cranial irradiation.

Subjects who were diagnosed between April 1994 and April 1996 were treated according to the ALL-BFM-90 protocol (26 Patients) and those who were diagnosed beyond April 1996 according to the ALL-BFM-95 treatment protocol (142 Patients). Patients were sub-grouped into two groups according to risk, 149 patients were characterized as medium -risk and 19 as high -risk. From the patients included in the HR group, 5 were treated with BFM-90 and 14 with BFM-95 (patients who underwent transplantation were excluded).

A retrospective analysis of patient data extracted from their charts was performed. Time points at which the data were grouped together were: a. Diagnosis b. End of treatment, c. One year and d. More than three years after completion of prescribed treatment. For patients relapsing after cessation of treatment, the data up to the time of relapse were eligible for analysis.

Data of thyroid function that was evaluated were: serum levels of the thyroid stimulating hormone (TSH), triiodo-thyronine (T3) and thyroxine (T4), anti-thyroidal antibody levels and imaging of the thyroid gland by ultrasonography.

Serum levels of TSH, T3 and T4 were measured with current high resolution commercially available assays. For the purpose of this study, thyroid dysfunction was defined as either a T4 value below or a TSH value exceeding the defined normal range. By this definition, thyroid dysfunction includes cases of clinical, subclinical and central hypothyroidism.

3. Results

Out of the 168 eligible patients, 141 had at least one evaluation of thyroid function following completion of treatment. This cohort of patients evaluated consisted of 78 males and 63 female patients. Thirteen were treated according to the ALL-BFM 90 Protocol (all were assigned to MR treatment group) whilst 128 were treated according to the ALL-BFM 95 Protocol (115 MR, 13 HR treatment group). In regards to radiotherapy, 21 patients received cranial irradiation at a dose of 12 Gy, except for one earlier patient who received 16.8 Gy.

3.1 Data at diagnosis of leukemia

At the time of diagnosis, one 12.6 year old female patient, with known Down syndrome (trisomy 21), had been diagnosed with hypothyroidism and was already receiving T4 supplementation for years. This patient was excluded from further analysis.

	TOTAL	
	N	%
Patients	141	
Age at Diagnosis		
Median	5.1	
Range	1.0 – 16.7	
Sex		
Male	78	55.3
Female	63	44.7
Treatment		
ALL-BFM 90	13	9.2
ALL-BFM 95	128	90.7
Treatment Group		
MR Group	128	90.7
HR Group	13	9.2
CT Only	117	83.0
CT + RT	24	17.0

Table 1. Patient Characteristics of the Eligible Patients.
Abbreviations: MR, Median Risk; HR, High Risk; CT, Chemotherapy; RT, radiotherapy

Twenty -seven patients have thyroid function data at diagnosis. Of those patients, 19 out of 27 had values of thyroid hormones and TSH within normal range and with appropriate ratio. Another 6 patients (2 males and 4 females) had low T4 with corresponding low TSH value. Free T4 (FT4) was not measured. Those 6 patients are considered to have low thyroid function due to critical illness, that is acute lymphoblastic leukemia. The corresponding T4 (in μg/dl) and TSH (in μIU/ml) serum values were 5.2/3.0; 2.9/1.1; 3.0/2.5; 6.3/0.2 respectively. The nonthyroidal illness syndrome or euthyroid sick syndrome, describes a condition characterized by abnormal thyroid function tests encountered in patients with acute or chronic systemic illnesses. The laboratory parameters of this syndrome include low serum levels of T3 and high levels of reverse T3, with normal or low levels of T4 and normal or low TSH. Thyroid function usually returns to normal as, the acute illness resolves.

Additionally two patients (1 male and 1 female) had compensated hypothyroidism (elevated TSH values with T4 values within the normal range) which resolved spontaneously, as the patients did not receive substitution therapy, and repeat thyroid function tests were normal.

Of interest is the case of a 7.3 years old girl who at diagnosis was found to have hypothyroidism as evidenced by elevated TSH (10.5 μIU/ml) and thyroid sonogram with echogenicity changes characteristic of thyroiditis Hashimoto. However, antithyroglobulin and anti-Thyroid peroxidase antibodies were negative. One month later and while on treatment with high dose steroids and chemotherapy, the T4 and TSH serum values of 11.7 (in μg/dl) and 10,5 (in μIU/ml) found at diagnosis were reduced to 3.9 and 0.7, respectively. This change was attributed to steroid administration. At the last follow up 6.5 years from diagnosis and 3.8 years after the end of treatment, she remains euthyroid (T4 6.19 μg/dl, T3 124.8 ng/ml and TSH 1.98 μIU/ml) with minor changes on ultrasound.

Furthermore, one male patient, 13.6 years old, during the maintenance treatment phase of chemotherapy, was diagnosed with compensated hypothyroidism, during laboratory investigation for bilateral femoral neck necrosis. At initial evaluation he was found to have TSH values of 6.5 μIU/ml with normal values of T4 and T3. On a 4 month follow-up, TSH value had increased to 7.8 μIU/ml and he was started on substitution therapy with p.o. levothyroxine. He was found to have positive anti-thyroglobulin antibodies while thyroid gland ultrasonography depicted minor echogenicity changes. Thus, he was diagnosed with compensated hypothyroidism 2.3 years after commencement of leukemia treatment, due to thyroiditis Hashimoto, and he continues to be on replacement therapy. This patient is excluded from further analysis.

3.2 High risk patients who received cranial irradiation

Out of the 168 eligible patients, 25 have received cranial irradiation. Out of the 141 evaluable, analyzed patients, 24 had received cranial irradiation as prophylaxis. Even though CNS leukemia was not apparent at diagnosis, the patients either belonged to the high risk group or were diagnosed with T-cell ALL and were irradiated according to the protocol mandates. Radiotherapy dose was 12 Gy for 24 patients and 16.8 Gy in one of the ALL-BFM 90 patients. Thyroid function data was available in all 24 patients at some time-point following initiation of treatment and in some patients with serial values. Thyroid function measurements were available at a median time of 7.8 years (range, 2.0 to 12.9 years) after initiation of treatment and at a median time of 4.6 years (range, -0.9 to 10.0 years) after completion of treatment. All patients had thyroid function within normal limits and no borderline values (median TSH value of 2.85 μIU/ml, range 1.1 to 4.1 μIU/ml). One patient had borderline low T4 with normal TSH, raising suspicion for hidden central hypothyroidism, but further evaluation with TRH or night TSH surge was not performed.

At the same time, 5 of 5 patients with thyroid ultrasound evaluation, normal thyroid gland size and architecture was appreciated. The patient who had received 16.8 Gy of cranial irradiation, had normal function at one year following cessation of treatment and no further evaluation. All patients who were evaluated for thyroid function (in total, all 5 and 12 patients evaluated for thyroid function) at the end of treatment (5 patients) and one year later (12 patients), were also found to have values within normal limits.

3.3 Medium risk patients treated with chemotherapy only

3.3.1 Data at the completion of maintenance chemotherapy

Thyroid function evaluation was available in a total of 38 patients, 25 boys and 13 girls, with median age at evaluation of 8.5 years (range, 5.1 to 17.5 years) and at a median time of 3.4 years (range, 2.7 to 4.3 years) after initial diagnosis.

Twenty- six from the 38 patients, 68.5%, had thyroid function evaluation within the normal range. That is, serum values of T4 above or equal to 7.0 μg/dl and TSH values lower than 5.0 μIU/ml. Sonographic evaluation of the thyroid gland was performed in four of those patients and revealed thyroid glands of normal size and architecture.

Two patients (1 male, 1 female, 5.2%) have evidence of compensated hypothyroidism (T4 4.74 μg/dl, T3 138 ng/ml and TSH 6.75 μIU/ml the first and 7.05 μg/dl, 143.2 ng/ml and 5.23 μIU/ml the second, respectively).

Moreover, 10 patients (7 male, 3 female, 26.3%) with low values of T4 and inappropriately low values of TSH were appreciated, and they are considered to have hidden central hypothyroidism, that has not been further investigated. Of those, two patients with repeated values have the same serum T4 and TSH findings at 2.1 and 3.0 years after the end of treatment. To the contrary, three patients with low values of both T4 and TSH at 2 to 3 months after the end of treatment, reversed to normal values (T4 above 7 μg/dl and TSH below 5 μIU/ml) at follow-up measurements 4 to 12 months from the previous evaluation.

In total, thyroid dysfunction was appreciated in 12 patients (8 males, 4 females) accounting for 31.5% of the patients at the completion of chemotherapy. Of the above 12 patients with evidence of thyroid dysfunction, 6 had imaging by ultrasound, at the same time that hormonal measurements were drawn. All had normal sonographic findings, without evidence of nodules or altered echogenicity indicative of thyroiditis.

3.3.2 Data at one to two years following cessation of the treatment of leukemia

Thyroid function evaluation was available in a total of 38 patients, 24 boys and 14 girls, with median age at evaluation of 9.6 years (range, 4.6 to 20.9 years) and at a median time of 4.5 years (range, 3.0 to 5.1 years) after initial diagnosis and at a median time of 1.3 years (range, 0.9 to 2.1 years) after the end of treatment.

Thirty -one patients (81.6%) had normal values for thyroid function. In this group are included 3 patients with compensated hypothyroidism at the end of treatment, who reversed to normal values without any intervention.

Four patients, 3 males and one female, (10.5%) had evidence of hidden central hypothyroidism (low values of T4 and TSH). In this group are included 2 patients who were considered to have hidden central hypothyroidism at the end of treatment and their values remained similar at the current time point.

Additionally, 3 patients, 2 male and one female, (7.9%) had evidence of compensated hypothyroidism (T4 in μg/dl, and TSH in μIU/ml values of 9.2/5.2, 7.2/6.9, 10.1/7.1 respectively).

In total 18.4% of the patients have evidence of thyroid dysfunction when evaluated one-two years, following completion of chemotherapy.

In this patient cohort belong 5 patients described before with measurements at the end of treatment. Of those, 3 patients had evidence of compensated hypothyroidism at the end of treatment time -point, that reversed at the one to two year measurement and also, 2 patients with hidden, possibly central hypothyroidism who remained with the same findings (low values of TSH and T4).

3.3.3 Data at more than three years following cessation of the treatment of leukemia

Thyroid function evaluation was available in a total of 77 patients, 40 boys and 37 girls, with median age at evaluation of 14.0 years (range, 7.7 to 24.0 years) and at a median time of 9.1 years (range, 5.2 to 15.7 years) after initial diagnosis and at a median time of 5.7 years (range, 3.0 to 12.5 years) after the end of treatment. Figure 2a illustrates the results for all 77 patients.

Sixty- eight patients (88%) had normal values for thyroid function. Within this group of patients we have identified a group of 13 patients, asymptomatic, with low normal values of TSH and T4 in the low portion of normal values, together with normal values of total serumT3, that are being closely followed for evidence of central hypothyroidism **(Figure 2c).**

	TOTAL		**End of Maintenance**		**1-2 years later**		**>3 years later**	
	N	**%**	**N**	**%**	**N**	**%**	**%**	**%**
Patients	141		38	26,9	38	26,9	77	54,6
Age at Diagnosis								
Median	5,1		5,1		5,0		4,9	
Range	1,0 – 16,7		2,1 – 14,5		1,1 – 16,7		1,1 – 13,1	
Age at Evaluation								
Median(years)			8,5		9,6		14,0	
Range (years)			5.1 - 17.5		4.6 - 20.9		7.7 to 24	
Time Following Diagnosis								
Median(years)			3,4		4,5		9,1	
Range (years)			1,7 – 4,3		3.0 - 5.1		5.2 - 15.7	
Time Following End of Treatment								
Median(years)			0,2		1,3		5,7	
Range (years)			-0,2 – 0,9		0.9 - 2.1		3.0 - 12.5	
Sex								
Male	78	55,3	25	65,8	24	63,2	40	51,9
Female	63	44,7	13	34,2	14	36,8	37	48,1
Patients with Normal Findings			26	68,5	31	81,6	68	88,3
Patients with Abnormal Findings			12	31,5	7	8,4	9	11,7

Table 2. Patient Results. Medium risk patients treated with chemotherapy only

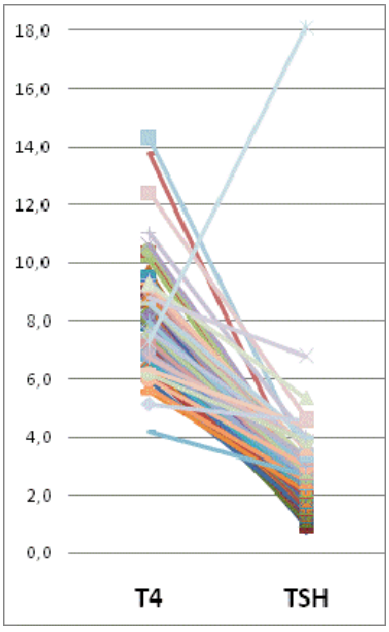
Interestingly, among these patients with normal thyroid function are two patients who reversed to normal values, as at two year follow-up were categorized as having compensated hypothyroidism, and have remained with normal values without any intervention up to 8.2 years later. The third female patient had increasing TSH values (from 5.2 to 6.8 μIU/ml) 3.9 years later and was referred to a local endocrinologist for further evaluation and treatment.

Two additional patients (a 24.4 year old female and a 13.7 year old boy) had previously been diagnosed with Hashimoto thyroiditis with borderline low T4 values and they were receiving p.o. treatment with levothyroxine at the time of last follow- up.

Additionally, a 15.8 year old girl had been receiving for a period of 6 months interferon-alpha 2b sc, as part of hepatitis C treatment and she was found to have TSH serum value of 18 μIU/ml. This is a possible side effect of the use of interferon-alpha. The medication was discontinued and the patient is being followed appropriately.

Furthermore, 6 patients (2 females and 4 males) were found to have low levels of serum T4 (less than 5.0 μIU/ml) together with normal to low normal values of TSH. These 6 patients are thought to have hidden central hypothyroidism. Three of them had normal thyroid sonograms. The patients need further evaluation with measurements of FT4, TBG to exclude TBG deficiency and depending on the results if FT4 is in the lower third of normal, perform a TRH test or measure TSH at night to assess whether there is normal night TSH surge, in order to exclude central hypothyroidism.

Among the group of patients with long- term follow- up 12% is found to have thyroid dysfunction of variable etiology.



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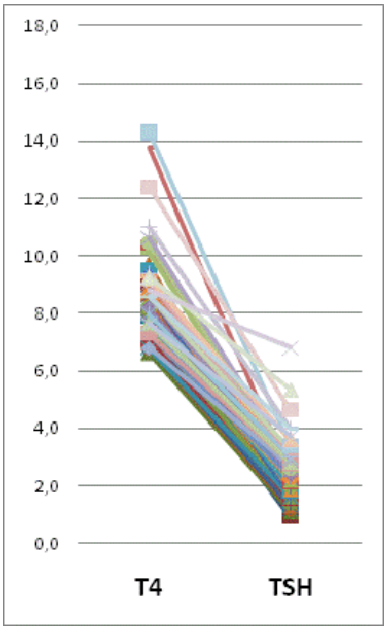

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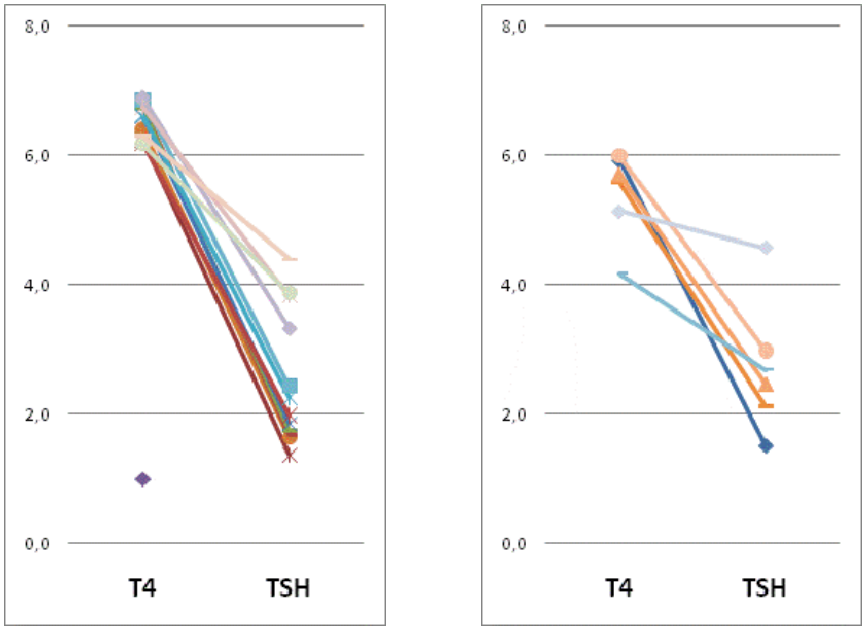

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Fig. 2. Relation of the values of thyroid stimulating hormone (TSH, in μIU/ml) and thyroxine (T4 in μIU/ml) of patients more than three years after the end of treatment.
A: All 77 patients; B: 57 patients with normal values; C: 13 patients with low normal values; D: 6 patients with low values.

4. Discussion

Improvements in therapeutic protocols for childhood acute lymphocytic leukemia has led to very high survival rates above 85% with current treatment protocols (Conter et al., 2010, Moricke et al., 2010, Pui et al., 2009, Pui et al., 2010). High survival rates have been confirmed in the current cohort of Greek patients treated in a single department using BFM-90 and BFM-95 (Papadakis et al., 2003).

Hence, it is of great importance first, to identify the long term effects of therapeutic modalities, chemotherapy alone or in combination with prophylactic cranial irradiation and second, to find ways to either prevent them or detect them at the earliest possible in order to treat them appropriately and timely, assuring improved quality of life. Complications from the endocrine system account for the majority of long term- sequelae of cancer therapy in childhood (Chemaitilly & Sklar, 2010). As acute lymphoblastic leukemia is the commonest malignancy of childhood, it is essential to study all the possible complications of the survivors.

To our knowledge, most of the papers published to date, include patients treated for childhood ALL, in larger cohorts of childhood cancer survivors (Madanat et al., 2008). In addition, there are studies referring selectively to ALL patients, including patients treated

with different protocols, as treatment guidelines were changing over time (Lando et al., 2001, Miyossi et al., 2008).

In this retrospective analysis, we aimed to recognize the prevalence of thyroid dysfunction in a cohort of Greek patients treated for childhood ALL, in a single center, according to the BFM-90 and BFM-95 treatment protocols. In the practice of this Center, as published previously (Papadakis et al., 2003), there are no patients assigned to the low risk group, meaning that a higher percentage of patients have received more intensive chemotherapy. Another factor that has to be appreciated, is that according to the current recommendations, the dose of cranial irradiation that the high risk group receives as prophylaxis of the central nervous system, is lower than the one administered in the previous decade. Furthermore, even smaller percentage of the patients treated for ALL are currently receiving cranial irradiation. An evaluation was performed at four time points as follows: at diagnosis, at the completion of chemotherapy, one to two years after completion of chemotherapy and at 3 years or later following completion of chemotherapy. Most of the previously reported data have no report on thyroid hormone values at diagnosis or at the end of therapy. The present data identifies the prevelance of thyroid dysfunction at all time points to occur at a relatively low percentage.

Of interest is the appreciation that a number of patients have thyroid dysfunction at diagnosis. A subgroup of the patients suffer from euthyroid sick syndrome related to the presence of a critical illness, that is acute lymphoblastic leukemia. Other patients have evidence of hypothyroidism or thyroiditis unrelated to the diagnosis of ALL. Therefore, we can suggest that evaluation of thyroid function which includes T4, FT4, T3, TSH as well as thyroid autoantibodies, should be added at the initial work-up, prior to chemotherapy initiation. Depending on the results, imaging of the thyroid gland by ultrasonography, has to be considered. This practice will permit us to identify thyroid dysfunction, preceeding therapeutic interventions, to assign specific etiology and differentiate among conditions that need to be treated, or euthyroid sick syndrome that usually needs no intervention and resolves spontaneously as the organism recovers.

As far as the high -risk group is concerned, which consisted of 24 patients who received intensified chemotherapy and cranial irradiation to12 Gy, thyroid function remains normal in the majority of subjects. As compared to previous reports, that radiation therapy increased the risk of hypothyroidsm development (Hancock, 1991) our findings can be attributed to the lower dose of radiotherapy that is administered as cranial and not craniospinal irradiation, thus exposing the thyroid gland to lower radiation dose. Data published previously, agrees that cranial radiation dose lower than 16 Gy is associated with lower risk of hypothyroidism development (Armstrong et al., 2010).

In the group of patients who were considered as medium- risk and received chemotherapy only we have appreciated the following findings. At the completion of chemotherapy, 68% of the evaluated patients have normal thyroid function. Of the patients who were considered to have some type of thyroid dysfunction, 5% have compensated hypothyroidism and 26% have possible hidden central hypothyroidism. It is of great interest that a third of them reversed to normal values 4 to 12 months later. These findings depict the importance of a more vigilant investigation to identify central hidden hypothyroidism using free T4 values, night TSH surge and in the patients that the results are equivocal, proceed to

thyroid releasing hormone (TRH) stimulation test. Although, it is evident that in a percentage of patients there is spontaneous recovery, it is meaningful to identify patients with central hypothyroidism and treat them appropriately. Thus, both growth impairment and metabolic complications such as dyslipidemia and obesity can be prevented and the patients' well- being can be improved. Re-evaluation will be desirable in order to reassess the need for treatment continuation.

At one to two years following completion of chemotherapy, normal thyroid function was found in 81.6% of the patients. Among those patients with normal thyroid function appreciated, there are patients whose values were abnormal at the one year follow-up. The remaining 18.4% had mild thyroid dysfunction of variable etiology. Compensated hypothyroidism represents 7.9% of the whole group, whilst the remaining patients with thyroid dysfunction are assigned to the possible central hypothyroidism diagnosis.

The majority of the patients in the chemotherapy only treated group have normal thyroid hormone values at the 3 years and beyond follow-up examination. In the normal function group are included patients that were diagnosed to have compensated hypothyroidism at the one to two year time point evaluation. Spontaneous improvement and normalization of the findings is seen. Among the patients with normal values, we have characterized a subgroup of patients who had T4 in the lower third of normal values and low corresponding TSH. This patient subgroup accounts for 14% of the group with normal values.

Furthermore, 12% of the patients, a substantial and not to be underestimated group of patients, had thyroid dysfunction of different etiologies. Included in this group is a 2.5% that has compensated hypothyroidism and 7.5% have possible central hypothyroidism. The patients with abnormal findings have no clinically appreciable symptomatology of hypothyroidism, besides some patients who were obese. However, there is no detailed recording of height measurements, lipid profile evaluation and body fat measurements, that could reveal a subtle or hidden central hypothyroidism.

A limiting factor of this study is the fact that all the patents do not have measurements at all time points so that we could have a complete picture of evolution of thyroid function and possible dysfunction. This is an inherent characteristic of a retrospective study, with data collected from patient chart recordings and not a prospective patient evaluation. Moreover, there are additional laboratory investigations that could have been applied in order to clarify the exact nature of the dysfunction seen, which have not been performed timely. It is conceivable that this has led to some bias in our analysis. Moreover, a complete investigation at diagnosis which can depict patients with thyroid binding globulin deficiency, ectopic thyroid that was missed, cases of dysormonogenesis or thyroiditis Hashimoto will facilitate the clarification of thyroid dysfunction post therapy.

As our aim was to identify all cases of clinical, subclinical and central hypothyroidism, without exploring the mechanism behind diminished thyroid function, we relied on the adequacy of TSH and T4 testing. There are no records of the exact prevalence of acquired hypothyroidism, in the general Greek population. If we compare the percentage of hypothyroidism in survivors of childhood ALL to that reported in other populations, like the Finnish population reported by Madanat et al (Madanat et al., 2007), we observe a higher percentage of ALL survivors with thyroid dysfunction.

The findings of this study support the idea that chemotherapy alone has untoward effect on thyroid function. The mechanism of inducing such a thyroid dysfunction remains unclear. Whether this is a direct side- effect of the chemotherapy applied or whether the thyroid function is impaired due to the diagnosis of ALL and the chronic insult of years of treatment, remains to be discovered. The fact that the radiotherapy applied does not increase the risk of thyroid dysfunction can be attributed to the lower dose of irradiation and the limited field of radiation (cranial RT only). The prevalence of thyroid dysfunction in this study is higher, as patients with borderline values of low T4 and corresponding low TSH values were included in the thyroid dysfunction patient group, in an effort to increase the awareness for the patients with possible central hypothyroidism. The study will be continued and further investigations will be carried out in order to calculate the exact percentage of hypothyroidism and clarify the etiology.

Hence, the observations and data presented in this study support the idea that thyroid dysfunction is encountered with increased frequency in survivors of childhood ALL. Serial measurements of thyroid hormones, as well as, search for signs and symptoms of hypothyroidism is imperative during the diagnosis and the short and long- term follow- up of ALL survivors.

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