INTRODUCTION

Most pediatric cancers are now curable with multiagent chemotherapy in combination with surgery and radiotherapy. The overall five years survival after diagnosis is now 75% for all pediatric malignancies ***(Aziz, 2002)***.

Intensive cytotoxic treatment of neoplastic diseases, has brought an increase of total remissions or even total cures in certain diseases, but also an increase of various complications resulting from toxicity of the treatment itself ***(Kavanaugh and Carbone, 1996)***.

One of the side effects of the use of cytotoxics is their suppressive effect on the immune system. Dysfunctions of the immune system are both of quantitative and qualitative nature and affect to a various degree all the essential elements of this system ***(Mazur, 2003)***.

It is believed that the construction of the immune system depends on length of treatment, type of treatment, and length of post-treatment period. Immunosuppression of the immune system may persist for many years following treatment with cytotoxics ***(Ohnishi et al., 1998)***.

T and B lymphocytes are depleted during intensive therapy, total immunoglobulin levels, particularly IgM are decreased. Previously attained immunity against various infectious antigens can be attenuated during therapy ***(Ek et al., 2004)***.

While receiving chemotherapy, patients have reduced numbers of helper cells ($CD4^+$cells) and suppressor cells ($CD8^+$ cells) and normal helper-to-supp-ressor cell ratios, indicating that helper and suppressor cells are equally affected by chemotherapy. After sto-pping treatment, prolonged significantly decreased levels of T4 cells, normal T8 cell levels and abnormal helper: suppressor cell ratios were found ***(Katz et al., 1987)***.

Further studies showed that NK cells were decreased while a patient was receiving chemotherapy and after treatment was stopped, with the number of NK lytic units either increased or decreased during the first six months off treatment, then falling to lower than normal levels ***(Ek et al., 2004)***.

Some childhood cancer survivors lose protective antibody levels against vaccine of preventable diseases, such as diphtheria, tetanus, invasive Hib infections, polio. The mechanism may be a general reduction of antibody-

producing cells in the bone marrow during chemotherapy ***(Abrahamsson and Mellander, 1997)***.

B lymphocyte function and T lymphocyte function usually recover 6 months after completion of chemotherapy, although recovery may take up to 1year. Normalization of Ig levels usually occurs after 1year ***(Mustafa et al., 1998)***.

However, impaired immune functions have been reported up to 5 years after treatment has ended. Even though immunoglobulin concentrations have regained normal levels, specific immunity may still be impaired and the patients could therefore be more prone to infections ***(Valur et al., 2001)***.

AIM OF THE WORK

The aim of this study is to:

A) Assess Cell mediated and Humoral immunity in childhood cancer survivors by:

1. Determining the lymphocyte subpopulations {the percentage of T helper/inducer ($CD4^+$ cells) and T suppressor/cytotoxic ($CD8^+$ cells) lymphocytes, $CD19^+$ B-lymphocytes}.

2. Determining serum protective antibodies levels of tetanus and diphtheria, and to investigate specific antibody response to tetanus and diphtheria vaccines for those with initially low titer.

B) To study the relation between the specific defects in the immune system and the type of the original disease and the chemotherapeutic regimen given.

C) To emphasis the importance of revaccination of childhood cancer survivors.

LONG TERM SURVIVORS OF CHILDHOOD CANCER

The treatment of childhood cancer has been increasingly successful over the past 30 years. Most pediatric cancers are now curable with multiagent chemotherapy in combination with surgery and radiotherapy. The overall survival five years after diagnosis is now 70% for all pediatric malignancies. With the sustained improvement in survival the number of long term survivors is increasing about 850 additional survivors of childhood cancer each year (***Wallace et al., 2001***).

Defining Cancer Survivorship:

Mullan, (1985) listed three stages: acute survival, extended survival, and permanent survival. Acute survival begins with a diagnosis and continues through the initial course of treatment. Extended survival is an intermediate stage, and it includes maintenance therapy and remission. The permanent stage (the long-term stage of survival) is a state of cure or sustained remission, without chemotherapy or after stoppage of chemotherapy. In this stage, the probability of disease recurring is greatly diminished.

Another group, ***Welsh McCaffrey and colleagues, (1989)*** also described the continuum of cancer survivorship. They laid out various cancer survivorship trajectories:

- Live cancer free for many years
- Live long cancer free, but die rapidly of late recurrence
- Live free of first cancer, but develop second primary cancer
- Live with intermittent periods of active disease
- Live with persistent disease
- Live with expected death

This model, again, is largely based on the bio-medical definition of cancer survivorship.

A theory of cancer survivorship is developing, and there are numerous assumptions that we can already put in place. First, survivorship is a dynamic concept that involves a continuum of events from diagnosis onward. Second, survivorship is experienced in five major ways: physically, psychologically, socially, behaviorally and spiritually ***(Clark and Stovall, 1996)***.

Long term sequales of pediatric cancer survivors:

The increased number of survivors has focused attention on the many long-term or late sequales of treatment. Late effects can be defined as any adverse effect that does not resolve after completion of therapy or any new problem that becomes evident after completion of therapy. Most of these effects are not detectable at the end of therapy but become evident with maturation (puberty), growth, and the normal aging process ***(Monteleone et al., 2006)***.

Mortality attributable to recurrence or progression of primary disease is decreasing, with increases in rates of mortality attributable to subsequent neoplasms, cardiac death, and pulmonary death largely due to treatment-related causes. In addition, the Childhood Cancer Survivor Study (CCSS) has identified specific treatment-related risk factors for late mortality. Radiotherapy, alkylating agents and epipodophyllotoxins increase the risk of death due to subsequent malignancy. Cardiac radiation exposure and high dose of anthracycline exposure are associated with late cardiac death ***(Armstrong et al., 2009)***.

Late endocrinal effects:

Chemotherapy, radiation therapy, and Hemo-poeitic Stem Cell Transplantation (HCT) can all result in impairment of endocrine function. The most significant endocrine complications are associated with radiation exposure but are also related to some chemotherapeutic agents ***(Monteleone et al., 2006).***

1- Neuroendocrinological disorders:

The hypothalamus is more radiosensitive and is damaged by lower doses of cranial radiation than the pituitary. Thus, after lower doses of cranial irradiation (<50 Gray (Gy)) the primary site of radiation damage is hypothalamic, and is usually associated with isolated Growth Hormone Defiency (GHD), whereas higher doses may also produce direct anterior pituitary damage which contributes to early and multiple pituitary hormone deficiencies ***(Monteleone et al., 2006).***

Hypothalamic-pituitary dysfunction secondary to radiation is also time dependent. There is an increase in the frequency and severity of hormonal deficits with a longer time interval after radiotherapy ***(Gleeson and Shalet, 2004).***

The progressive nature of the hormonal deficits following radiation damage to the hypothalamic-pituitary axis can be attributed to the delayed effects of radiotherapy on the axis or the development of secondary pituitary atrophy following previous hypothalamic damage ***(Schmiegelow et al., 2000).***

The damaging effects of radiation on hypo-thalamic-pituitary axis function are also increased when the hypothalamic-pituitary axis is already affected by pathology. A radiation dose of 35-42.5Gy to the hypothalamic-pituitary axis caused isolated GHD in the majority of children treated for non-pituitary brain tumours, whereas a similar dose in adult patients irradiated for pituitary adenomas led to multiple pituitary hormone deficits in more than 80% within a similar time scale after radio-therapy ***(Monteleone et al., 2006).***

Clinical observations reveal that growth hormone (GH) is the most radiosensitive followed by gonadotrophin and adreno-corticotrophin (ACTH) with thyrotrophin (TSH) the last hormone to be affected, although variations in this order can occur ***(Gleeson and Shalet, 2004)***.

Effect on growth and development:

Growth failure in childhood cancer survivors is caused by:

- Cranial irradiation
- Radiation to growth centers (e.g., in bone marrow transplant recipients)
- Radiation to the spine
- Inadequate weight gain
- Chronic unresolved illness
- Depression
- Hormone deficiency
- Hypothalamic-pituitary disorders secondary to tumor, surgery, chemotherapy, or cranial irradiation.

(Landier et al., 2004)

Chemotherapy has been associated with a variable risk of short stature, puberty has been noted to take place at a significantly younger age after RT, but does not significantly affect final height, whereas delayed puberty has also been associated with decreased upper segment to lower segment ratio, presumably due to decreased sex steroid hormone production ***(Noorda et al., 2001***).

Other parameters known to influence final height outcome in cancer survivors include the patient's

genetically determined height potential and other concomitant hormone insufficiencies, such as hypothyroidism ***(Gurney et al., 2003$_b$)***

Growth hormone deficiency (GHD) is a common dose and site-related sequele following radiation to the brain. The incidence of GHD is 100% in children who receive more than 4500 Centigray (cGy) for optic chiasm gliomas and up to 75% in children who receive 2900-4500cGy for medulloblastoma. As many as 50% of children who receive 2400cGy prophylactic cranial irradiation (CRT) for ALL develop GHD during the year or two after treatment, while those who receive 1800cGy are less prone to GHD (0-14% incidence). Although most children recover adequate hormone levels, they do not experience catch-up growth ***(Monteleone et al., 2006)***.

Tantawy and Coworkers, (2002) reported that the survivors of childhood cancer had a lower relative for age basal growth hormone secretion, however not statistically significant compared to controls, and that cranial irradiation with a dose of 1800cGy was associated with normal spontenous growth hormone secretion.

Additionally, younger age at the time of radiotherapy (RT) has consistently been associated with a strong risk for

short adult height, as has treatment with RT during rapid pubertal growth ***(Oberfield and Sklar, 2004)***.

More than any other factor, however, irradiation of the spine has been implicated in a high risk of short adult height. This is probably due to damaged growth plates after high doses of radiation. Patients treated with spinal RT are consistently shorter than those treated with cranial RT alone with reduced response to Growth Hormone releasing hormone (GHRH) or normal endogenous GH levels ***(Shulamit et al., 2004)***.

Abdel-Ghany et al. (2006) found higher percentages of patients with Ht percentiles below 3rd centiles in survivors of ALL who received both chemotherapy and CRT (62.5%) compared to those who received only chemotherapy. However there were no significant difference between survivors of solid tumors who received chemotherapy and CRT (16.7%) and those who received chemotherapy alone (10%).

2- Thyroid dysfunction:

Thyroid dysfunction, manifested by primary hypothyroidism, hyperthyroidism, goiter, or nodules, is a common delayed effect of radiation therapy fields that include the thyroid gland incidental to treating Hodgkin's lymphoma, brain tumors, head and neck sarcomas, and acute lymphoblastic leukemia (ALL) ***(Oeffinger and Hudson, 2004)***.

Of children treated with radiation therapy, most develop hypothyroidism within the first 2 to 5 years post treatment, but new cases can occur later. Reports of thyroid dysfunction differ depending on the dose of radiation, the length of follow-up, and the biochemical criteria utilized to make the diagnosis ***(Sklar et al., 2000)***.

Criteria for diagnosis of hypothyroidism, (the most frequently reported abnormality), include elevated thyroid-stimulating hormone (TSH), depressed thyroxine (T4), or both Compensated hypothyroidism includes an elevated TSH with a normal T4 and is asymptomatic. Uncompensated hypothyroidism (Overt hypothyroidism) includes both an elevated TSH and a depressed T4 ***(Gleeson et al., 2002)***.

Compensated hypothyroidism (i.e., elevated thyroid-stimulating hormone (TSH), normal thyroxine levels)

occurs in 14-75% of children irradiated for Hodgkin disease with doses of 4000cGy or more and about 9% of children who receive prophylactic CRT with doses greater than or equal to 2400cGy for ALL. Overt hypothyroidism occurs in 16-21% of Hodgkin disease patients and 2% of ALL patients after radiation with 2400cGy ***(Monteleone et al., 2006)***.

Ionizing radiation penetrating the thyroid gland also induces nodule development and thyroid cancer. Thyroid cancer, predominantly papillary or follicular adenocarcinoma, was diagnosed at 18 times the expected rate for the general population. Females were at increased risk for hypothyroidism and thyroid nodules ***(Oeffinger and Hudson, 2004).***

Khalifa et al. (1986) found no abnormalities in thyroid function tests in the studied group of patients (24 survivors of ALL, 14 received chemotherapy and prophylactic cranial irradiation, 10 received chemo-therapy only). ***Abdel-Ghany et al. (2006)*** reported normal thyroid function tests in their studied group of cancer survivors except for 10% who had high TSH and normal T4, only one patient, who received mantle radiation, had low T4 and high TSH but was asymptomatic.

Survivors of pediatric HSCT are at increased risk of thyroid dysfunction, with the risk being much lower (15%-16%) after fractionated TBI, as opposed to single-dose TBI (46%-48%). Non-TBI-containing regimens do not appear to increase risk. While mildly elevated TSH is common, it is usually accompanied by normal thyroxine concentration ***(Brennan and Shalet, 2002).***

Thyroid replacement is recommended even in those with compensated hypothyroidism because chronic stimulation of the thyroid gland by elevated TSH has been suggested, but not proven, to increase the risk of secondary thyroid cancer in humans. It has also positive implication for cardiac, gastrointestinal and neurocognitive function ***(Monteleone et al., 2006).***

3- Gonadal dysfunction:

I- Early puberty

The mechanism for early puberty following irradiation is thought to be due to the disinhibition of cortical influences on the hypothalamus. Puberty then proceeds through the increased frequency and amplitude of gonadotrophin-releasing hormone (GnRH) pulsatile secretion by the hypothalamus ***(Roth et al., 2001)***.

Low-dose cranial irradiation employed in central nervous system prophylaxis for ALL is associated with a