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Endocrine sequelae of cancer and cancer treatments

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Abstract
Introduction Exposure to cancer and its treatments, including chemotherapy and radiotherapy, may result in late adverse effects including endocrine dysfunction. Endocrine disorders are the most commonly reported long-term complications of cancer treatment, especially by adult survivors of childhood cancers. This review will explore the endocrinologic adverse effects from non-endocrine cancer therapies.
Methods Searches including various Internet-based medical search engines such as PubMed, Medline Plus, and Google Scholar were conducted for published articles.
Results One hundred sixty-nine journal articles met the inclusion criteria. They included case reports, systematic analyses, and cohort reports. Endocrine disorders including hypothalamus dysfunction, hypopituitarism, syndrome of inappropriate anti-diuretic hormone secretion, diabetes insipidus, growth hormone disorders, hyperprolactinemia, gonadotropin deficiency, serum thyroid hormone-binding protein abnormalities, hypothyroidism, hyperthyroidism, hypomagnesium, hypocalcemia, hyperparathyroidism, hyperparathyroidism, adrenal dysfunction, gonadal dysfunction, hypertriglyceridemia, hypercholesterolemia, diabetes mellitus, and glycosuria were identified and their association with cancer therapies were outlined.
Discussion/conclusions The journal articles have highlighted the association of cancer therapies, including chemotherapy and radiotherapy, with endocrine dysfunction. Some of the dysfunctions were more often experienced than others. Especially in patients treated with radiotherapy, some endocrinologic disorders were progressive in nature.
Implications for cancer survivors Recognition and awareness of endocrine sequelae of cancer treatments may permit for early detection and appropriate follow-up care for cancer survivors, thus improving their overall health and quality of life.

Keywords Endocrine system · Drug effects · Endocrine system diseases · Chemically induced · Complications · Antineoplastic agents · Adverse effects · Radiotherapy · Adverse effects · Late effects

Introduction

The continued progress in detecting cancer and in understanding its biology, the advent of new chemotherapeutic agents, the refinement of diagnostic techniques, and the improvement of surgical methods have resulted in enormous advances in cancer survival rates. In the USA, there are more than 10 million cancer survivors, nearly 4% of the national population. Cancer survivorship has become part of the mainstream society, leading to the Institute of Medicine's and the National Research Council's recommendations for the long-term follow-up of cancer survivors and for research in this area [1].

To systematically analyze the health profiles of various groups of cancer survivors so that appropriate strategies can be developed for their ongoing health care, the Life After Cancer Care (LACC) program was launched at The University of Texas M.D. Anderson Cancer. LACC mem-

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bers have published information on the long-term effects from cancer treatment [2–8], including diabetes [9] and thyroid problems [10].

Exposure to systemic chemotherapy and radiotherapy, although improving survival rates, can carry several unwanted and persistent health effects long after therapy is completed. These long-term effects are varied, and can include neurologic, cardiovascular, musculoskeletal, gastrointestinal, genitourinary, integumentary, pulmonary, and endocrinologic problems, (e.g., neuroendocrine dysfunction).

Many excellent published studies exist to describe the long-term adverse effects of childhood cancer treatments. However, documentation about the adverse endocrinologic effects of therapy on survivors of adult cancers is limited. The development of therapy-based endocrine disorders depends on the total dose, the duration of exposure, and the interval since the completion of therapy. The varying survival rates amongst studies have resulted from many factors, including abnormalities present before treatment; multiple confounding treatments such as spinal irradiation, glucocorticoids, and chemotherapy drugs that inhibit cell growth; multiple diagnoses; and differing analytic hormonal testing methods [11]. Many research studies on the adverse effects of cancer therapy on the endocrine system were published decades ago when cancer management was more aggressively focused on securing survival. However, more recent regimens have been more carefully tailored to reduce the potential for short- and long-term adverse effects. The focus of this present review is endocrinologic adverse effects from non-endocrine cancer therapies.

Susceptibility to the toxic effects of therapy differs amongst the endocrine glands because of the individual glands' cellular characteristics. Certain endocrine organs, such as the testis, experience high rates of cell division, which makes them more sensitive to the toxic effects of antineoplastic drugs and irradiation. In other cases, the drug may target a biosynthetic pathway, making cells that use these pathways susceptible to injury. Another variable is the distribution of the chemotherapeutic agent, which depends on factors such as lipophilicity, metabolism, the elimination rate of individual drugs, and the ability of a particular endocrine tissue to absorb the drug. Glands that receive a higher concentration of a drug are more likely to manifest adverse effects of that drug [12].

Adult survivors of childhood cancers are more likely to experience endocrine dysfunction than are survivors of adult cancers. Collectively, endocrine disorders are the most common long-term complications of cancer treatment [13]. In a study conducted at Memorial Sloan-Kettering Cancer Center, the most common sequelae in a cohort of 650 adult survivors of childhood cancers were endocrine complications, reported by 40% of those survivors. The most commonly reported of these disorders were growth hormone (GH) deficiency, primary hypothyroidism, and primary ovarian failure [14]. Among survivors of neuroblastoma, 80% reported late endocrine effects including thyroid and gonad dysfunction [15]. Other studies demonstrated that 20% to 50% of childhood cancer survivors reported endocrine disturbances [11].

Published reports are generally fragmented and consist primarily of case reports, small-cohort reports, and information provided by pharmaceutical manufacturers. We therefore undertook an intensive, up-to-date search using various Internet-based medical search engines, including PubMed, Medline Plus, and Google Scholar. We encountered some challenges because therapy protocols continue to evolve with the advent of novel drugs. It is important to reemphasize that many of the studies were conducted over a decade ago when researchers were interested in the side effects of chemotherapeutic drugs and radiotherapy, and they have not been re-addressed since then. Some of the therapy regimens or drugs have been discontinued however we felt it was of merit to include their late effects for this review. We have attempted to include most endocrine dysfunctions and their associations with cancer drugs and radiotherapy, as reported by cancer survivors. Table 1 lists the endocrine sequelae outlined in this paper and the treatments that were identified in published studies to play a role in bringing about the sequela.

Disorders of the pituitary gland

Hypothalamic dysfunction

It is generally believed that chemotherapy alone does not induce hypothalamic-pituitary dysfunction; although Rose et al. [16], in a cohort of 31 patients who had had childhood cancer, showed that hypothalamic dysfunction could occur in survivors of non-central nervous system tumors who received chemotherapy instead of radiotherapy. Malignancies in the vicinity of the hypothalamic-pituitary axis are often treated with surgery and/or radiotherapy, with systemic chemotherapy being reserved for recurrent tumors or as a palliative measure [17].

The hypothalamus is more sensitive than the pituitary to the effects of radiation. Hypothalamic pituitary dysfunction resulting from irradiation of the cranial region may be delayed and can linger for many years. Reports have suggested that the number of pituitary deficiencies increases with the length of time since the time of radiotherapy [18].

Surgery to remove malignancies such as craniopharyngiomas in the hypothalamic region may also result in hypothalamic dysfunction.

Table 1 Endocrine sequelae and the treatments that were identified to play a role in bringing about the sequela

Sequelae	Potential and attributed treatment
Hypothalamic dysfunction	Radiotherapy, surgery, possibly chemotherapy
Hypopituitarism	Interferon, radiotherapy
Syndrome of inappropriate anti-diuretic hormone syndrome	Vinca alkoids, cisplatin, cyclophosphamide, melphalan
Diabetes insipidus	
Nephrogenic	Ifosfamide, Streptozocin
Central	Radiotherapy, surgery
Growth hormone (GH) secretion disorders	Radiotherapy, with or without chemotherapy, glucocorticoids, and surgery
Hyperprolactinemia	Carmustine, vincristine, methotrexate, and radiotherapy
Gonadotropin deficiency	Untreated hyperprolactinemia, irradiation, and surgery
Serum thyroid hormone-binding abnormalities	L-asparaginase, estrogens, tamoxifen, mitotane, fluorouracil, alkylating agents, and podophyllin
Hypothyroidism	Cytokines, sunitinib, tyrosine kinase inhibitors, and radiation
Hyperthyroidism, including Grave's disease	Radiotherapy, cytarabine, daunorubicin, and cytokines
Hypomagnesemia	Cisplatin, amphotericin B, cyclosporine, possibly carboplatin
Hypocalcemia	Cistplatin, interferon, surgery, and rarely radiotherapy.
Adrenal dysfunction	Mitotane, glucocorticoids, busulfan, suramin, and possibly irradiation
Gonadal dysfunction	Radiotherapy, some alkylating agents, some nitrogen mustards, doxorubicin, vinblastine, and bleomycin
Hypertriglyceridemia	Retinoids and interferons
Hypercholesterolemia	Retinoids, asparaginase, glucocorticoids, and cyclosporine
Diabetes mellitus	Interferons, glucocorticoids, l-asparaginase, vacor, alloxan, streptozocin, cyclosporine, temsirolimus
Glycosuria	Methotrexate, cistplain, and ifosfamide

Hypopituitarism

Hypopituitarism is not as common for survivors of adult non-pituitary brain tumors as it is for survivors of childhood non-pituitary brain tumors [19]. Two reports of interferon-induced hypopituitarism have been published [20, 21].

Besides surgery, radiotherapy for malignancies in the craniospinal region is often used; this therapy has been a frequent but underestimated cause of pituitary deficiency in survivors. Hypopituitarism is one of the most commonly reported complications after radiotherapy to the hypothalamus-pituitary axis. Agha et al. [19] demonstrated that 41% of 56 adult patients who underwent radiotherapy for non-pituitary brain tumors exhibited hypopituitarism: 16% had a single hormone deficiency and 25% had multiple deficiencies. In another follow-up study [22], after a median of 10.5 years, 87 patients who had undergone postoperative radiotherapy for pituitary macroadenomas were monitored for pituitary dysfunction: 97% exhibited hypopituitarism, 61% had panhypopituitarism, and 88% had other radiation-induced pituitary disorders; in addition, 87% needed hormone replacement therapy to alleviate their symptoms.

Hypopituitarism can also result from progressive late toxicity. In one study [23], in which patients underwent radiotherapy for acromegaly, hypopituitarism was present in 33% of a cohort of patients at baseline; it then increased to 57% at 5 years, 78% at 10 years, and 85% 15 years after treatment. This late toxicity has been reported in other studies as well [24, 25].

Syndrome of inappropriate anti-diuretic hormone secretion (SIADH)

Toxicity or nerve impairment to the posterior pituitary gland may result in the inappropriate production and secretion of antidiuretic hormone (ADH), also known as arginine vasopressin. SIADH has long been associated with cancer therapy [12]. Cytotoxic treatments that may cause SIADH include vinca alkoids, cisplatin, cyclophosphamide, and melphalan [13, 26–30]. Syndrome of inappropriate antidiuretic hormone (SIADH) may also present as an endocrine paraneoplastic syndrome. Tumors, usually of neuroendocrine origin, may produce excessive amounts of ADH [31].

Diabetes insipidus

Nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus may result from the effects of ifosfamide or streptozocin (formerly called streptozotocin) on tubular reabsorption of water. There are published studies of ifosfamide-induced Fanconi syndrome with nephrogenic diabetes insipidus, even in children [32–34]. Streptozocin has also been associated with cases of nephrogenic diabetes insipidus that were reversible [35, 36]. Although both ifosfamide and Streptozocin produce cytotoxic effects on renal tubular cells, the cellular mechanism of nephrogenic diabetes insipidus is not clearly outlined [12]. To our knowledge, no new reports on nephrotoxicity from antineoplastic drugs have been published in the past decade.

Central diabetes insipidus

Unlike anterior pituitary dysfunction, central diabetes insipidus has not been diagnosed in survivors of childhood tumors who underwent radiotherapy to the hypothalamic–pituitary axis [37]. Borson-Chazot and Brue [38] concluded that initial radiation impairment occurs in the hypothalamus but that diabetes insipidus is never observed. However, central diabetes insipidus was reported for the first time in 2004 in a patient who had undergone surgery and megavoltage irradiation for a pituitary tumor [39].

Central diabetes insipidus frequently occurs from pituitary or hypothalamus malignancies and from surgery or cranial irradiation to these regions [40].

GH secretion disorders

GH deficiency, a commonly reported complication of childhood cancer and cancer treatment, is the most frequently observed endocrine deficiency in long-term survivors of childhood cancers treated with cranial irradiation. Adults with GH deficiency resulting from primary hypothalamic-pituitary disease during childhood often experience increased adipose mass, decreased lean mass, as well as decreased strength, exercise tolerance, bone mineral density, and quality of life [41].

Chemotherapy has also been implicated in GH deficiency. Román et al. [42] reported that 44% of a cohort of 25 children who had received chemotherapy and surgery for malignant solid tumors developed impaired GH secretion. Findings from a study of children treated with or without adjuvant chemotherapy after radiotherapy for medulloblastoma revealed that the addition of chemotherapy, including lomustine, vincristine, methotrexate, or cytosine arabinoside, may intensify the negative effects of radiation on GH secretion [43]. In addition, treatment with glucocorticoids such as dexamethasone completely suppressed the secretion of GH in another study [44].

The effect of radiation on GH deficiency is dose related [37]. Borson-Chazot and Brue [38] also determined that after brain irradiation, somatotropic function is the first condition affected, with 90% of patients becoming GH-deficient within 10 years after treatment. GH deficiency may occur after low-dose irradiation and may not appear for at least 10 years after treatment [45]. More recently, GH deficiency was diagnosed in 30% of 249 child survivors of cancer in an Australian study, 62% of whom had been treated with irradiation [46]. This follows an earlier study that demonstrated that 97% of a cohort of children who had been treated with cranial irradiation for brain tumors developed GH deficiency [47].

Hyperprolactinemia

Hyperprolactinemia is one the most common disorders of the hypothalamic-pituitary axis [48]. Dopamine from the hypothalamus normally inhibits prolactin secretion from the pituitary gland; cranial irradiation, however may interfere with this inhibition, resulting in hyperprolactinemia. This disorder, is rare in children, and of unclear clinical significance [13]. Hyperprolactinemia has been described in both sexes and in patients of all ages; but it is seen most frequently in young women after intensive radiotherapy and is usually subclinical [49].

In one study, seven out of a cohort of eight patients who had received chemotherapy (including carmustine, vincristine, and methotrexate) concurrent with radiotherapy for brain tumors displayed hyperprolactinemia [50]. However, Constine et al. [50, 51] concluded that the influence of carmustine chemotherapy on the likelihood or severity of radiation injury to cranial tissues was not known. In addition, the frequency of endocrinologic dysfunction in patients who received carmustine was not statistically different from that of patients treated with radiation alone [50, 51].

Hyperprolactinemia has also been reported after radiotherapy to the hypothalamic–pituitary region, which, likely impairs the hypothalamus, resulting in deficiency of the endogenous prolactin inhibitory factor [52]. High-dose cranial radiotherapy, especially doses greater than 50 Gy, to the hypothalamus region has been associated with hyperprolactinemia [11, 50].

Gonadotropin deficiency

Gonadotropin deficiency refers to either the absence or loss of luteinizing hormone and follicle-stimulating hormone. The loss of gonadotropin function has been recognized as an effect of both chemotherapy and radiotherapy. In adults,

gonadotropin deficiency may cause sex steroid hormone deficiency and infertility [12]. Women may experience amenorrhea and men may experience impotence and lack of libido.

Untreated hyperprolactinemia may interfere with the secretion of gonadotropin by the pituitary and decrease the responsiveness of the pituitary to gonadotropin-releasing hormone; this can cause gonadotropin deficiency, which can ultimately lead to secondary hypogonadism [53].

Agha et al. [19] determined that 27% of the men who had received cranial radiotherapy for primary brain tumors experienced gonadotropin deficiency. However, the Constine et al. [51] study demonstrated that gonadotropin deficiency is experienced by up to 61% of patients treated with irradiation for brain tumors. Cohen [11] determined that radiation doses greater than 35 Gy to the hypothalamus-pituitary axis may result in gonadotropin deficiency. Another study [54] noted that 31% of a cohort of children treated with high-dose radiation for head and neck tumors developed gonadotropin deficiency. The incidence of gonadotropin deficiency increases with time since irradiation, with a cumulative incidence of 20 to 50% reported in patients at long-term follow-up, making it the second most common anterior pituitary hormone deficiency [54].

Surgical methods to remove tumors embedded in the hypothalamus region may injure the hypothalamus, and in turn can cause gonadotropin deficiency.

Disorders of the thyroid gland

Serum thyroid hormone-binding protein abnormalities

L-Asparaginase appears to inhibit the biosynthesis of thyroxine (T_4)-binding globulin, at least in vitro [55]. Increased levels of T_4-binding globulin found in patients taking estrogens and tamoxifen, mitotane, and fluorouracil led to elevated levels of total T_4 [56–58]. Small decreases in T_4-binding globulin were observed in a cohort of patients treated with alkylating agents and podophyllin [59]. The chemotherapeutic effects on thyroid hormone-binding proteins have not been extensively studied in recent years.

Hypothyroidism

The effects of chemotherapy and endocrine treatment on thyroid function are still being debated. Young age and the addition of chemotherapy to treatment regimens were reported to be associated with a higher incidence of hypothyroidism. Primary hypothyroidism is seen more frequently than central hypothyroidism [60].

Treatment with cytokines has also been linked with primary hypothyroidism. In a study of low-dose interleukin-2 for melanoma, 14 of 55 patients (25%) experienced thyroid dysfunction, attributed to autoimmune thyroiditis [61].

Bohbot et al. [62] reported that interferon alfa may induce thyroid autoimmune disease, and an earlier published report demonstrated that the frequency of thyroid dysfunction from interleukin-based immunotherapy ranged from 15 to 91% [63].

Primary hypothyroidism is a frequent complication of sunitinib, a novel tyrosine kinase inhibitor used for malignancies such as renal cell carcinoma and gastrointestinal stromal tumors. Studies have revealed incidences of hypothyroidism resulting from sunitinib use of 30 to 85%. This complication has been attributed to sunitinib's effect on the thyroid endothelium, which results in thyroid dysfunction [64–70]. Another tyrosine kinase inhibitor, sorafenib, has also been associated with hypothyroidism. However, Maitland and Ratain [68] stated that to their knowledge, no prospective studies of thyroid function in patients being treated with sorafenib were under way as recently as 2006.

Bexarotene is a retinoid-X receptor-selective ligand used to treat patients with cutaneous T-cell lymphoma. Central hypothyroidism (low serum thyrotropin and T_4 concentrations) is a frequent complication of bexarotene [71]. To date, this is the only form of selective central hypothyroidism induced by pharmacologic agents in humans.

The most common adverse effect from irradiation to the thyroid gland is primary hypothyroidism, in both its overt form (with a low T_4 level and elevated thyroid-stimulating level) and compensated form (with a normal T_4 level and elevated thyroid-stimulating hormone level) [11].

Cranial and spinal irradiation, alone or in combination, can also compromise thyroid function, leading to hypothyroidism and increased risk of malignant thyroid nodules [38, 72].

Radiotherapy alone and combined with chemotherapy is associated with a higher risk of thyroid dysfunction than is chemotherapy alone. Craniospinal irradiation, compared with total body irradiation (TBI) or direct thyroid irradiation was found to be less harmful to the thyroids. Female patients were more sensitive than male patients [73].

Radiation-induced thyroid dysfunction may include primary or central hypothyroidism, Graves' disease, thyroiditis, euthyroid Graves' ophthalmopathy, benign adenomas, multinodular goiter, and radiation-induced thyroid malignancies. The most common radiation-induced thyroid late effect, primary hypothyroidism, affects 20 to 30% of patients treated with radiotherapy to the neck area [73].

The association between radiotherapy and thyroid dysfunction in cancer survivors has been outlined in other publications [74–76]. Ishiguro et al. [77] reported progressive thyroid dysfunction in a subset of patients treated with bone marrow transplantation during childhood and con-

cluded that thyroid dysfunction is contingent on age at transplantation with greater risk in younger patients.

Hyperthyroidism, including Graves' disease

Several groups have reported the development of hyperthyroidism in adult cancer survivors who had undergone radiotherapy to the neck area, especially those treated for Hodgkin's disease; the prevalence of hyperthyroidism exceeded that seen in the general population [78–80].

Al-Anazi et al. [81] described a patient who developed reversible Graves' disease after an induction course of chemotherapy with cytarabine and daunorubicin for acute leukemia. Recent studies have summarized cases of hyperthyroidism and Graves' disease induced by interferon alfa therapy [82, 83]. Chianese-Bullock et al. [61] also reported that 13 of 55 patients who were treated with interleukin-2 for melanoma developed hyperthyroidism: this condition reversed in most patients after treatment was discontinued.

The symptoms of hyperthyroidism experienced by survivors who have received radiotherapy to the neck area are similar to those of Graves' disease: diffusely enlarged thyroid gland, elevated level of thyroid hormone, suppressed level of thyroid-stimulating hormone, increased thyroidal uptake of radioactive iodine, and development of auto antibodies to the thyroid [84, 85].

Sklar et al. [84] reported that the overall incidence of hyperthyroidism in survivors of Hodgkin's disease was eight times greater than that reported in sibling controls and the risk of hyperthyroidism was dose-dependent.

Parathyroid disorders

Hypomagnesemia

Three drugs have been associated with clinically significant hypomagnesemia: cisplatin, amphotericin B, and cyclosporine. In addition, carboplatin was described as "potentially significant" in inducing this disorder. These agents may also bring about hypokalemia and hypocalcemia [86]. Elisaf et al. [87] reported that one of the most common causes of hypomagnesemia is cisplatin administration. Studies have tended to refer to episodes of hypomagnesemia in terms of treatment cycles rather than by patient numbers, and percentages of incidences have ranged from 20% in a 1997 study to 100% in an older study [86, 88].

In one study, 651 patients with sarcoma were followed up for an average of 2 years after treatment. Hypomagnesemia was found in 12.1% of patients after cisplatin therapy and in 15.6% of patients after carboplatin therapy, in contrast to 4.5% of patients not given platinum-based treatment [89].

Hypocalcemia

Hypocalcemia is another complication of chemotherapy. The effects of cisplatin on renal tubular function, magnesium metabolism, bone resorption, and vitamin D metabolism may induce hypocalcemia [53, 90].

Tumor lysis syndrome (TLS) is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. It is frequently seen in patients with hematologic cancers but has also been observed in patients with solid tumors such as hepatoblastoma and advanced neuroblastoma. A total of 45 cases of TLS were documented between 1977 and 2002 in patients with solid tumors. TLS was observed after single-agent or combination chemotherapy in 31 (68.9%) of those 45 patients. TLS has also been reported after radiotherapy alone or in combination with chemotherapy, after surgery, after endocrine therapy with corticosteroids and tamoxifen, after treatment with biologic response modifiers plus interferon, and as occurring spontaneously. However, TLS was found most frequently in patients with metastatic disease and with tumors highly sensitive to antineoplastic therapy [91].

In other studies, some patients being treated with interferon for malignant tumors, including metastatic carcinoid tumors, exhibited hypocalcemia [92, 93].

Hyperparathyroidism

The first association between irradiation and hyperparathyroidism was reported in 1975, and subsequent investigators have confirmed the association [94–96]. Studies have shown a latency period of 35 to 49 years between radiation exposure and clinically significant hyperparathyroidism, and findings support the hypothesis that hyperparathyroidism develops more rapidly in patients treated with radiation as adults than as children [95–97]. Hypercalcemia and/or hyperparathyroidism has not been associated with surgery.

Hypoparathyroidism

Hypoparathyroidism is a frequent complication of treatment against squamous cell carcinomas of the larynx and hypopharynx because of the proximity of the parathyroid glands to these structures. Both surgery and radiation therapy have been associated with this complication. In a report from South Africa up to 63% of patients treated with surgery and 88% of patients treated with only radiation therapy were prone to develop hypoparathyroidism in a 5-year period of follow-up [98].

Adrenal dysfunction

The adrenal gland is often overlooked in terms of screening and testing for endocrine disruption [99]. Symptoms of adrenal insufficiency may include malaise, fatigue, weakness, anorexia, nausea, vomiting, weight loss, abdominal pain, diarrhea, hypothermia or hyperthermia, hypotension, altered mental status, and coma [100]. Such symptoms often overlap with symptoms of cancer or cancer therapy and adrenal deficiency may be overlooked.

Mitotane can induce primary adrenal insufficiency through its adrenolytic activity [101]. Since it must be administered in large doses in order to be therapeutic, it may destroy both normal and malignant adrenocortical cells; suppressed glucocorticoid secretion and increased glucocorticoid metabolism may also occur [102–104].

Several reports from as early as the 1960's have documented the effects of busulfan on adrenal function [105–107]. Busulfan therapy may create a clinical syndrome similar to adrenal insufficiency [107–109].

Glucocorticoid therapy is prescribed as replacement therapy in patients treated with mitotane or busulfan on the adrenal glands or after adrenal surgery. The most frequent cause of secondary adrenal insufficiency in patients with cancer is prolonged glucocorticoid treatment as primary cancer treatment or for symptomatic relief. Suppression of the hypothalamus pituitary axis by glucocorticoids may render the adrenals atrophic [100, 103].

Although adrenal toxicity has been observed in animals treated with sunitinib, no overt clinically significant adrenal suppression has been reported by patients taking the drug. However, physicians are encouraged to monitor their patients for potential subclinical adrenal toxicity [110].

Suramin, a growth factor antagonist often used in the treatment of adrenocortical and prostate cancer, may also suppress adrenal function [111, 112].

Constine et al. [50] reported that the frequency of pituitary or hypothalamic hypothyroidism and hypoadrenalism in patients treated with irradiation for brain tumors not involving the pituitary gland is generally lower than 5%.

Megestrol acetate is a progestational agent used to treat patients with endometrial and breast cancer and to improve appetite in patients with wasting syndromes. This agent has steroid activity that may suppress pituitary ACTH production and abrupt withdrawal may cause central adrenal insufficiency [113].

Gonadal dysfunction

Radiotherapy and chemotherapy may result in transient or permanent testicular or ovarian dysfunction. Gonadal function is permanently impaired in patients receiving intensive chemotherapy or TBI-containing regimens [114]. The gonads are sensitive to radiation, and the degree of impairment depends on the field of treatment, total dose, and therapy schedule.

Gonadal dysfunction has been reported as the most common long-term adverse effect of chemotherapy, especially in survivors of childhood tumors [115]. Gonadal toxicity is dose-dependent and can be induced by alkylating agents (including procarbazine, cisplatin, and vinblastine) and gonadotoxic drugs (including doxorubicin, cyclophosphamide, melphalan, and chlorambucil). Isolating the toxicity of individual drugs is difficult because they are often administered in multi-agent regimens [13, 116–118].

In males, germ cells are more sensitive than Leydig cells to the effects of cytotoxic agents [119] and therefore react differently to individual anticancer drugs. The effect of cytotoxic drugs on Leydig cell function has been recognized, but its clinical significance is not clear, especially in pubertal boys [53, 120–122]. However, if used in high doses, chemotherapy may produce toxic effects in Leydig cells [123]. Alkylating agent-based regimens can also induce Leydig-cell dysfunction; in fact, 10 to 57% of male patients have displayed elevated levels of luteinizing hormone after treatment [124]. Some studies have also revealed azoospermia with raised levels of follicle-stimulating hormone in the majority of patients treated with alkylating agents or procarbazine [124–127]. Bramswig et al. [128] determined that the addition of procarbazine to a chemotherapy regimen induced a toxic effect on spermatogenesis and possibly Leydig cell toxicity in a considerable number of German patients; however, the toxic effects of etoposide and cyclophosphamide could not be demonstrated.

Weichno et al. [129] determined that in a cohort of 326 men treated with cisplatin for testicular cancer, the most common endocrine abnormality was elevated gonadotropin levels; 55% had elevated levels of luteinizing hormone, and 49% had increased levels of follicle-stimulating hormone, and lowered testosterone levels. In a subset of survivors of testicular cancer who had undergone cisplatin-based chemotherapy in an earlier study, 63% had elevated serum levels of follicle-stimulating hormone, 24% had elevated levels of luteinizing hormone. [130].

Vinblastine-based regimens such as PVB (cisplatin, vinblastine, and bleomycin) have resulted in a higher incidence of gonadal toxicity than etoposide-containing regimens; increased toxicity was also found in patients who had received both vinblastine and etoposide for testicular cancer [127].

The speed of spermatogenesis recovery depends on the radiation dose and schedule [11]. Since the germinal epithelium is extremely sensitive to radiotherapy, the effect on spermatogenesis can occur with very low doses, with

infertility reported to occur at fractionated doses higher than 2 Gy [119]. Howell and Shalet [125] could not determine a radiation dose threshold above which permanent azoospermia is inevitable.

In another study published in 1997, Arlt et al. [131] demonstrated that 47% of male survivors who had undergone irradiation for brain tumors exhibited erectile dysfunction, as opposed to 6% of the controls: in addition, 32% had hypothalamic hypogonadism, and 10% had primary gonadal dysfunction. Since then there have been no published similar case-study reports confirming Arlt's demonstration.

In women, cyclophosphamide has been identified as the drug most responsible for causing chemotherapy-related amenorrhea. The higher the cumulative dose of cyclophosphamide, the higher the incidence of ovarian failure [132, 133]. Chemotherapy induces amenorrhea, sometimes resulting in permanent infertility and/or vaginal atrophy, depending on the patient's age and drug dosage; and may also accelerate menopause [116, 134].

The prevalence of chemotherapy-induced amenorrhea has ranged from 21 to 71% in women younger than 40 years and from 49 to 100% in women 40 years of age and older [135–138]. The addition of tamoxifen to adjuvant chemotherapy regimens may increase the incidence of amenorrhea [121]. In addition, older age and the addition of taxane to therapy regimens are more likely to result in irreversible chemotherapy-induced amenorrhea [117].

Pelvic irradiation in women may also interfere with ovarian function. Oocytes in the mature follicles are more sensitive to radiation damage than are oocytes in primitive follicles; therefore, cessation of ovarian function is also dependent on the radiation dose and the age of the patient [139].

Tauchmanova et al. [140] studied a group of 40 survivors who had been treated with allogeneic bone marrow transplantation and a regimen of busulfan and cyclophosphamide without TBI. The most common endocrine dysfunction (reported by 95% of patients) was ovarian insufficiency. Another report demonstrated that with fractionated TBI doses of 15 Gy or higher, all patients experienced ovarian failure [141]. TBI is more toxic to ovaries in patients older than 25 years. Meistrich et al. [142] studied that in a cohort of girls treated with radiation to the spine for brain tumors and found that 35% displayed increased gonadotropin levels, resulting in primary ovarian dysfunction.

Lipid metabolism disorders

Hypertriglyceridemia

Retinoids, including 13-*cis*-retinoic acid, and other vitamin A derivatives, and retinoid X receptor agonists like bexarotene often induce hypertriglyceridemia [143]. High levels of serum triglycerides were noted in 38% of patients taking interferon alfa and *cis*-retinoic acid and undergoing radiotherapy for high-grade gliomas [144].

Isotretinoin (a 13 *cis*-retinoic acid) elevated plasma triglyceride levels in 20% of patients in another study [145]. In this study, young adults who had previously developed high triglycerides during isotretinoin therapy for acne had an increased risk of future truncal obesity, hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia, and hyperuricemia [145]. Stoll et al. [146] demonstrated that isotretinoin increased plasma triglyceride levels but did not change insulin sensitivity.

Elevated triglyceride levels have been reported in patients treated with interferons, including interferon alfa-2a [147]. The effect of interferon-alfa on hypertriglyceridemia was first noted by Peñarrubia et al. [148] in 1995 in a cohort of patients with chronic myeloid leukemia. Hypertriglyceridemia is more frequently experienced with a longer duration of interferon therapy [149].

Hypercholesterolemia

There is no consensus regarding the effects of cisplatin on serum cholesterol levels. Raghavan et al. [150] and Gietema et al. [151] showed an increased level of serum cholesterol in patients who had received cisplatin-containing therapy for testicular cancer. In contrast, Fenton et al. [152] in a later study could not determine an association between cisplatin-based chemotherapy and lipid profiles.

Agents that affect lipid metabolism, such as mitotane, retinoids and asparaginase, also induce hypercholesterolemia [153–155]. Mitotane apparently induces cholesterol synthesis that seems to respond adequately to treatment with statins [154]. Studies using bexarotene, in patients with lymphoma, revealed that hypercholesterolemia was a frequently reported adverse effect [156, 157]. Asparaginase is often prescribed in conjunction with corticosteroids for hematological malignancies, and the combination may induce severe hyperlipidemia, including hypercholesterolemia in patients with acute lymphoblastic leukemia [158–161].

Hypercholesterolemia has been observed in a study using prednisolone and other long-term steroid-based regimens [162]. Cyclosporine use has also been associated with hypercholesterolemia, both in human trials [163], and in trials with mice and rats [164, 165].

Disorders of glucose metabolism

Diabetes mellitus

The role of cytokine synergism in diabetes mellitus is a complicated one and several studies have attempted to

identify which cytokines that induce pancreatic cell apoptosis. One study determined that the synergistic effects between interferon gamma and tumor necrosis factor alpha, rather than the Fas ligand, are responsible for apoptosis of the pancreatic islet cells, both in vitro and in vivo [166]. In one series, the adverse effects of interferon therapy included glucose intolerance or onset of type 1 diabetes mellitus, especially in patients being treated for hepatitis C [167–170]. The first case of type 1 diabetes that developed during interferon alfa therapy was reported in 1992 [168]. Fabris et al. [171] reported that interferon therapy may bring about insulin-dependent diabetes in patients with a predisposition to diabetes mellitus.

Diabetes mellitus has also been frequently diagnosed in survivors of acute lymphoblastic leukemia who had been treated with glucocorticoids and L-asparaginase. Glucocorticoids induce insulin resistance, whereas L-asparaginase may affect insulin metabolism and sensitivity; however, a combination of these factors may increase glucose intolerance synergistically [172, 173].

Certain drugs may cause transient hyperglycemia, whereas streptozocin, alloxan, and Vacor are likely to produce permanent diabetes [174]. The effect of streptozocin on diabetes mellitus was first reported in 1974 [175]. Pavel et al. [176] determined that 30% of patients who took doxorubicin and streptozocin for neuroendocrine tumors developed adverse effects, including diabetes, renal failure, and encephalopathy.

Cyclosporine has also been implicated in inducing hyperglycemia [177]. Sestier et al. [178] suggested that the addition of cyclosporine to low-dose streptozocin in mice enhanced the toxicity of diabetes induced by the streptozocin. However, cyclosporine alone also induced glucose intolerance associated with beta-cell degranulation and high pancreatic cyclosporine content [178].

Hyperglycemia has also been induced in 6 to 69% of patients using the recently approved drug, temsirolimus, used to treat renal cell malignancies and neuroendocrine tumors [179–181].

Glycosuria

Some cancer survivors treated with high-dose methotrexate, cisplatin, and high-dose ifosfamide have developed glycosuria as a progressive phenomenon. The percentage of patients with glycosuria increased from 23% at first evaluation after chemotherapy to 72% during the follow-up period ranging from 9 to 49 months after completion of chemotherapy. Age did not seem to be a risk factor [182].

In an earlier study, treatment with ifosfamide was associated with glycosuria. Skinner et al. [183] reported that glycosuria was the most common urinary abnormality in a cohort of children and adolescents treated with ifosfamide for various malignancies, occurring in 88% of the patients.

Summary

Endocrine dysfunctions are recognized adverse effects of anti-cancer therapy. Certain late effects may not develop for many years after treatment, especially in patients treated with cranial irradiation, while others may develop early and linger for many years.

The National Comprehensive Cancer Network has developed more than 100 clinical guidelines since the mid 1990s to cover most of the clinical sequelae seen in cancer survivors [184]. Unfortunately no existing guidelines are detailed for endocrine specific sequelae of cancer and cancer treatments.

As cancer therapy continues to evolve over the years with the advent of novel drugs and regimens, previously unreported late effects experienced by cancer survivors will continue to emerge. A recent report from the Institute of Medicine report *From Cancer Patient to Cancer Survivor: Lost in Transition* (1) calls for the improving of existing guidelines that address earlier regimens and for adopting new evidence-based guidelines to address current and future treatment regimens.

The endocrine system is exquisitely sensitive to many antineoplastic modalities. Diagnosis and treatment of endocrine dysfunctions is generally available and effective.

There is a dearth of recently published studies on endocrine effects, including gonadotropin deficiency, of certain cancer treatments which may be addressed by continued research. As indicated in this review, there are several conflicting reports on certain late effects and hopefully further research will clarify these.

Awareness of potential endocrine sequelae of cancer treatments can, therefore, allow for the early detection and appropriate treatment of cancer survivors, thus improving their general health and quality of life.

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