Rehabilitation of Cured Leukemia Patients - Physician's Role

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ABSTRACT

Improvements in therapy and early detection using advanced techniques have increased survivorship in leukemia. But at the same time this has unmarked some serious toxicities stemming from the consequences of radiation or chemotherapy. Development of second malignancies are an imposing problem. Radiation is perhaps the main culprit but chemotherapy has its share. Anthracycline chemotherapy can cause irreversible cardiac damage. With the advent of echo Doppler study, nuclear imaging and biochemical markers, early detection of such cardiac dysfunctions are possible. In patients receiving cranial radiation and chemotherapy, chronic neurocognitive effects are especially challenging and may be assessed by IQ sources or by assessment of academic achievements. There are now methodologies to improve neurocognitive dysfunction by functional and pharmacologic interventions. Thus after primary treatment, leukemia survivors will be incorporated into mainstream population and will be followed up more commonly by their physicians. The latter who being in direct contact with these patients should develop a clinical acumen to identify these complications at the earliest in order to successfully rehabilitate them into the mainstream socially, physically and psychologically.

INTRODUCTON

As improvements in treatment and early detection of cases continue to accumulate in oncology, we are blessed with the problem of needing to understand the long term consequences of cancer survivorship. It is clear that more and more of our leukemia patients are surviving longer and longer. They have unique problems that we need to recognize and be able to participate, detect early and try to prevent. Among these are problems stemming from the consequences of treatment, including chemotherapy or radiation therapy. There is continued elevated risk for the development of future cancers and other chronic problems in these patients who otherwise would have succumbed to the leukemias. Three decades ago when President Nixon declared a 'war on cancer' in the US, long term survival from leukemias was seldom expected and patients were often not even told their diagnosis. Much has changed in the ensuing decades. Long term follow up of survivors of leukemias has produced considerable knowledge regarding specific adverse outcomes, including second malignancies, cardiotoxicity, hypothalamic – pituitary endocrinopathy, neurocognitive and neuropsychological effects.[1,2] The childhood cancer survivor study (CCSS) has been one of the most well conducted studies to gain knowledge of long term effects of cancer and its therapy.[3]

SECOND PRIMARY CANCERS

There are several reasons for which second primary cancers develop in a leukemia survivor. Whatever reasons predisposed a given patient to develop the initial cancer would also predispose the patient to develop the second cancer e.g. genetic predisposition or shared environmental risk factors. It is interesting that when one thinks of second malignancies, the issue on which most people focus is treatment effects. Of treatment effects, cranial radiation is perhaps the main culprit in inducing second cancers like brain tumors. Use of alkylating agents or etoposide for chemotherapy may induce second leukemias and cyclophosphamide may induce bladder cancer. It is necessary for the physicians to know about these facts because most of the leukemia survivors will be incorporated into mainstream population and will be followed up more commonly by their physicians than by oncologists. Being in direct contact with these patients having a high index of suspicion physicians can pick up these complications earlier.[4] Thus physicians have an obligation to educate survivors and provide follow up care for such delayed effects to enable their proper rehabilitation into social and occupational mainstream.

REPRODUCTIVE DYSFUNCTIONS

Cytotoxic properties of chemotherapy or radiation therapy may harm the gonads and affect the fertility of cured patients. There

might be premature ovarian failure or precocious puberty on one hand and azoospermia on the other hand.

Males

Leydig cells are more resistant than germ cells to chemotherapy. In young adults, semen monitoring has become standard methodology to follow up populations at risk. Normal sperm counts should be >20 x 10^6/ml and standard WHO classification of dyspermia is used. Oligospermia or azoospermia reflect states that may be transitory because recoveries are observed after 10 years calling for repeated tests. Oligospermia does not mean 'infertility' because spontaneous pregnancies occur with <5 x 10^6 spermatozoa/ml. Ejaculatory azoospermia does not mean testicular azoospermia; testicular sperm extraction is possible and may be followed by intracytoplasmic sperm injection. Not much is known about spermatogenesis in prepubertal boys after chemotherapy. However, the observations in adults apply to pre- and peripubertal boys; alkylating agents are most toxic than other agents while anticancer antibiotics (like doxorubicin) and antimetabolites are least toxic. It should be mentioned that plasma FSH level and sperm analysis do not strictly reflect actual and potential fertility status of the individual survivor.

Substitutive hormonal therapy is rarely required except only in cases of clinical insufficiency, biologically confirmed by an abnormal plasma LH response to LH-RH stimulation. The minimal plasma testosterone needed to warrant normal sexual function is $\geq$ 10nmol/L. No major risk of cancer was found in offsprings of male leukemia survivors and after natural conception no excess of congenital malformations was found. Thus it is the responsibility of attending physician to arouse curiosity in these patients regarding fertility and sexuality and to help them find answers from reproductive medicine specialists.

Females

At conventional chemotherapy doses the ovarian follicle is more resistant than spermatogenesis and most women preserve their ovarian functions. In cases of preserved follicles, taking into account the risk of relapse, pregnancy should be advised as quickly as possible if a child is desired. The physicians must also reassure that there is no contraindication to lactation in a cured leukemia survivor. Indeed, girls in their early reproductive life who would postpone pregnancy until education or professional goals have been achieved should be advised, to enter into early pregnancy.

Regarding offsprings of female leukemia survivors, most series eventually show results that are reassuring without any increased incidence of malformations or genetic damage.

CARDIOTOXICITY

Anthracycline chemotherapy can cause irreversible cardiac damage in leukemia survivors. Although many of them appear to be well, they may be compensating either physiologically or by altering their lifestyles, for some degree of heart damage. Early recognition and treatment by the physicians may increase survival and quality of life of these patients.

Thus survivors of leukemia who have received potentially cardiotoxic therapies require regular repeated evaluation of cardiac status even if they are asymptomatic. Several regimens have been suggested e.g. Late Effects Screening Guidelines produced by the Children's Oncology Group, but no specific regimen has been validated for efficacy and cost effectiveness. Testing intervals of 1 to 3 years appear to be sensible and justifiable. The physician moreover must remember to exercise caution in events that may augment already decompensated cardiac function like starting a heavy isometric exercise programme, growth hormone therapy, pregnancy, undergoing anaesthesia and so on.

Delayed anthracycline–related cardiac decompensation has been documented to occur as late as 20 years after treatment.[5] The risk of chronic cardiac dysfunction may be greatest for those who developed echocardiogram abnormalities during or immediately after completion of therapy. Electrophysiologic changes, LV dysfunction, decreased exercise capacity and congestive cardiac failure may develop. Children tend to show combined dilated and restrictive disease while adults typically display purely dilated disease. When cardiotoxicity is of late-onset, it is often asymptomatic. Late occurring, rapid-onset, severe cardiac decompensation is rare amongst these cancer survivors and most often are due to arrhythmia or infarction.

Risk of anthracycline induced cardiotoxicity increases with cumulative dose (> 400 –550 mg/m^2), extremes of age, smoking and comorbidity (like obesity, hypertension and family history of ischemic heart disease).

Besides from the usual investigations for cardiac dysfunction (e.g. echocardiogram, Holter monitoring, nuclear imaging i.e. MUGA scan), there are other varieties of laboratory tests of proven or investigational value. C-reactive protein, lipoprotein(a), fibrinogen and homocysteine are recognized for their potential to identify high risk individuals for an ischemic heart disease. Other potentially relevant tests include tests for brain natriuretic peptide (BNP), insulin and insulin-like growth factor-1, free T4/thyroid stimulating hormone and estradiol/testosterone, depending on risk factors.

ENDOCRINE ABNORMALITIES

Thyroid abnormalities are expected in leukemia survivors due to the cranial radiation therapy leading to pituitary dysfunctions or due to altered immune status of these patients. These abnormalities include hypothyroidism or hyperthyroidism of which hypothyroidism is commonest and frequently needs thyroid hormone supplementation. Thus the physician must be very much aware to detect these at the earliest (even subclinically) as they are very well manageable and will improve the quality of survivorship.

Growth impairment has been reported in leukemia survivors due to cranial irradiation leading to growth hormone deficiency or due to gonadal dysfunction (like premature or delayed puberty) particularly in girls. Physicians need to monitor growth charts of these children and adolescents; and growth hormone should be administered whenever required.

NEUROCOGNITIVE DISORDERS

In patients receiving cranial irradiation and/or chemotherapy, chronic neurocognitive effects are especially challenging.[6,7] Historically, intelligence quotient (IQ) scores have provided a benchmark against which to measure changes in cognitive development after treatment. Observed declines in IQ are most

likely as a result of failure to learn at a rate that is appropriate for the age of the child, rather than from a loss of previously acquired knowledge. The rate of IQ decline is associated with several risk factors, including younger age at the time of treatment, longer time since treatment, female sex and other relevant clinical variables. Loss of cerebral white matter and failure to develop white matter at a rate appropriate to the developmental stage of the child could partly account for changes in IQ scores. Technical advances in radiotherapy hold promise for lowering the frequency of these sequelae and there are several options now available to do away with prophylactic cranial radiotherapy in at least some subsets of patients.

Physicians need to be aware of the different methodologies that monitor neurocognitive dysfunctions like neuroimaging, IQ testing and assessment of academic achievements. Presently, knowledge-based measures of IQ and academic achievement are viewed as the distant indicators of core cognitive functions such as attention, speed of processing and working memory which provide the foundation for evaluation of cognitive dysfunction in childhood and adult survivors of leukemia.

Physicians may try cognitive remediation and pharmacotherapy for cognitive dysfunction. Studies on cognitive remediation include compensatory memory notebook that would improve neurocognitive function in an adolescent with severe memory impairment. The most systematic effort to apply ideas of cognitive remediation in children with neurocognitive deficits is the programme developed by Butter, Copeland and Colleagues which is a tripartite model that uses techniques and methods from three disciplines: brain injury rehabilitation, special education and clinical psychology. Other methodologies that attending physicians may suggest for rehabilitation of these patients is cognitive – behavioural psychometry, stress management and reinforcement of realistic, positive and optimistic self-statements. Intervention at the level of school ecology may also be helpful. It is also the duty of the physician to explain the affected areas of neurocognitive defects to patients, their parents and teachers.

Research done over the past 50 years in children diagnosed with attention deficit hyperactivity disorder (ADHD) who are otherwise healthy has shown the effectiveness of stimulant medications like methylphenidate to improve cognitive performance.

PSYCHOSOCIAL ISSUES

In long-term leukemia survivors there are nearly three areas of psychosocial morbidity.

1. Physical problems e.g. fatigue, concerns about appearance, troubles in eating and physical restrictiveness.
2. Psychological problems including fears about future, anxiety and depression.
3. Community reintegration problems including difficulty in resuming social relations, stigmatization, financial and employment difficulties.

Physicians need to recognize these and send the patients for suitable counselling.

CONCLUSION

Physicians play an important role in the attempt by oncologists to rehabilitate the survivors of leukemia into the mainstream socially, physically and psychologically. The aim is to add "life to years" and not merely "years to life". We have only won the battle uptil now by curing the leukemia but the war or crusade against leukemia is still going on with the aim to improve the quality of life during their survivorship.

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