Editorial-I

Gonodal Toxicity of Cytotoxic Chemotherapy: the Price of Cure !

Cure rates for cancer have increased progressively over last three decades. For young adults who are long term survivors gonodal toxicity is an important issue.

Both neoplastic disease and its therapy can interfere with normal sexual and reproductive biology. Primary cancer in the testis and ovary or metastasis to genitourinary system or the hypothalamus and pituitary can interfere with normal functioning of reproductive organs. Similarly, procedures like retroperitoneal lymphadenectomy for testicular cancer and bladder neck surgeries can interfere with ejaculation. However, the greatest adverse effects on sexual and reproductive biology are due to the use of cytotoxic chemotherapy and radiation. In potentially curable malignancies like Hodgkin's lymphona (HL), acute lymphoblastic leukemia, non Hodgkin's lymphoma (NHL), bone and soft tissue sarcoma, breast cancer and testicular cancer[1] Survival rates are approaching close to 80%, reproductive dysfunction remains a significant concern.

In young men the differentiating spermatogonia proliferate rapidly and are hence maximally susceptible to the effects of cytotoxic chemotherapy. However, the Leydig cells which produce androgens and Sertoli cells which are supporting cells survive most cytotoxic chemotherapies but may sustain functional damage. Hence the eventual recovery after chemotherapy depends on the ability of the spermatogonial stem cells to regenerate and differentiate into adequate sperms capable of fertilization. Inhibin, that is secreted by the Sertoli cells and androgen secreted by the Leydig cells have feedback inhibition on the follicle stimulating hormone (FSH) and luteinising hormone (LH) secretion by the hypothalamus and pituitary. Hence testicular failure and infertility after chemotherapy are assessed by measuring the sperm count, FSH and LH levels after therapy.[2]

In women, the primordial follicles, which are finite in number are recruited during the time of ovulation. Depletion of primordial follicles secondary to cytotoxic chemotherapy is manifested as premature amenorrhoea. However, transient ovarian dysfunction secondary to damage of maturing follicles or poor follicular recruitment, stress, weight loss and malnutrition that influence hypothalamic activity and estrogen metabolism can manifest as temporary amenorrhoea. As in men FSH and LH levels are sensitive indicators of sub optimal ovarian function.

In this issue of the IJMPO, Mushtaq Ahmed and colleagues have reported the findings of their study on the gonodal toxicity of CHOP, COP and COPP chemotherapy in 60 men with HL and NHL between the ages of 16-42 years with a follow up of more than 2 years.[3] They have used the standard parameters of FSH & LH levels along with the sperm counts pre and post therapy. Pre treatment infertility was present in 13.3% of patients with, but the differences in the pre-treatment sperm counts, FSH & LH were not significantly different between patients with HL and NHL. The salient finding reported is the prolonged azospermia and sub normal testicular function as reflected by the persistently elevated FSH and LH in patients receiving COPP. Their major conclusion is that cyclophosphamide and procarbazine containing regimens are most gonadotoxic. The recovery rates following CHOP regimen at 25% was lesser than the 66.6% reported in the literature.[4] The other important points brought

out by this study are that although there is steady recovery in the sperm counts beyond 2 years, recovery is unlikely after 5 years and that recovery of sperm counts is better in patients <30 years compared to >30 years.

However, it is important to realise that normal sperm counts are not always associated with fertility and that men with oligospermia can father children without assistance.[5] Moreover other problems in men like erectile dysfunction and loss of libido post chemotherapy can contribute substantially to the problem of infertility.[6] These parameters have not been assessed in the study. Longer follow ups and assessment of sexual quality of life parameters could throw more light on these issues.

Since the time that cure rates for certain cancers have plateaued, there has been a steady progress in minimising long term adverse events associated with treatment. The total replacement of COPP/MOPP regimens by ABVD has ensured that almost 100% of patients recover their sperm counts compared to about 20% with COPP/MOPP.[7] Similarly fewer chemotherapy cycles for patients with good risk early stage NHL and nerve sparing retroperitoneal lymph node dissection (RPLND) in patients with Stage I testicular cancer are some examples.[8]

Sperm banking needs to be discussed right at the beginning before initiation of gonadotoxic chemotherapy.[9] Sperm banking is an expensive procedure and may be beyond the reach of most patients. Also assisted reproductive techniques like 'in vitro' fertilization and intra cytoplasmic sperm injection have limited success in the range of 30-40%.[10] Hence, for patients in whom fertility is an important concern, minimising therapy, alternative less gonadotoxic regimens and surveillance wherever possible need to be considered.

As with most things in life, long term survivals after cancer comes at a price and gonodal toxicity is just one of them. With rapid strides in therapy, we can only hope that these long-term adverse events will be reduced to a minimum and the price to pay will be less.

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