

MEDICAL MANAGEMENT OF MALIGNANCIES

Cancer is a genetic disease resulting from the mutations, either inherited or acquired, altering the normal genes to abnormal 'oncogenes'. These in turn lead through a complicated cascade of biochemical signals to uncontrolled proliferation of the affected cells, which have the properties of **autonomy** (independent growth), **metastasis** (spread to other organs), **dysplasia** (altered structure of the cell) and **clonality** (same origin of cells). These malignant cells lead to death of the patient by uncontrolled growth, widespread metastasis, malnutrition, and other systemic effects. For earliest clinically detectable tumor, 10^9 cells are required and 10^{12} cells for death of the patient. To achieve cure, all these cells must be eliminated and presence of a single cell, at the end of treatment, can lead to recurrence and death (Skipper's postulates).

Contrary to popular belief, cancer is a systemic disease with metastasis occurring during the pre-clinical growth of the tumour. Hence the small tumors usually have widespread metastasis at the time of diagnosis though they cannot be detected by clinical examination or investigations. This has become the basis of **multi-modal treatment** of cancers consisting of **surgery, radiotherapy, chemotherapy, immunotherapy, and endocrine therapy**. Of late, **genetic therapy** has been added to the therapeutic armamentarium. While surgery and radiotherapy are **loco-regional** modalities, medical therapy aims at **systemic** treatment. Cancer being a systemic disease requires treatment for the local as well as systemic spread as treating local and regional disease will result in subsequent systemic failure.

Chemotherapy is of several types depending upon the intention of treatment and timing of administration. The term 'primary chemotherapy' is used when it is the main stay of treatment in conditions such as in leukemia and lymphoma. It is termed as '**curative**' when used with intent of cure; '**palliative**' when used for symptomatic relief such as pain, dysphagia; and **salvage** when used for treatment of a recurrent or residual disease.

Depending upon the **timing** in respect to surgery or radiotherapy it can be adjuvant or neoadjuvant. When administered after the resection of the tumour of the tumour it is known as **adjuvant** chemotherapy and aims to eliminate the residual microscopic disease to prevent subsequent distant metastasis. Classical example is breast cancer where surgery eliminates the cancer in the breast and the axillary nodes but not the microscopic cells left in the various places as liver, bone, lung or elsewhere. These remaining cancer cells (micro-metastasis) if untreated will grow into larger lesions subsequently and result in obvious clinical systemic metastasis. Chemotherapy attempts to eliminate these micro-metastases and thus improves the cure rates by preventing the clinical metastasis.

Neoadjuvant chemotherapy is administered **before the surgery** with a several aims of **limb or organ conservation** or making an **unresectable tumour** to a **resectable tumour**. Limb conservation is practiced in osteosarcoma of femur where the standard treatment has been amputation or disarticulation of the limb. With pre-operative administration of chemotherapy, the tumour can be shrunk, so that a limb sparing surgery can be carried out in the patient. Similar principle is applied in tumours of larynx resulting in preservation of voice. In advanced ovarian cancer with massive intra-abdominal spread, it may not be possible to resect the tumour and administration of chemotherapy results in shrinkage of this tumour (chemo-debulking) and after few cycles she can undergo surgery with good results. Carcinoma of breast, rectum, stomach and many solid tumours can be managed similarly. However, it must be remembered that in some patients the response may not be adequate to achieve the desired response resulting in tumour progression and death. Such people have the disadvantage of losing the chance of primary treatment as well.

Chemotherapeutic drugs act on rapidly multiplying cells at various intra-cellular structures or inhibit DNA or RNA or protein synthesis leading to cell death. They cannot distinguish between normal and the cancer cells and hence both will be affected in resulting in shrinkage of the tumour as well as side effects due to the death of normal cells. Most commonly affected cells are that of bone marrow, mucous membrane and hair follicles leading to well-known complications of bone marrow depression, mucositis and alopecia. In addition vomiting (emesis), hepatic, renal, cardiac, pulmonary and CNS dysfunction are commonly encountered. After the administration of the first cycle, subsequent cycle is administered only after recovery of bone marrow, to prevent further toxicity, which takes about three weeks. This is the basis of three weekly chemotherapy cycles and when there is prolonged effect of the drugs the cycle may be repeated after four or six weeks. With each cycle a fraction of cancer cells are eliminated hence to achieve a cure many such cycles are required. The treatment duration and the drugs will vary according to the malignancy.

Administration of chemotherapy: Prior to initial administration of chemotherapy all patients must be counselled about chemotherapy and informed consent obtained. Investigations include complete blood counts, renal and hepatic parameters in all patients and cardiac evaluation in some. Co-existing diseases like diabetes and hypertension must be noted and managed. Effective anti-emetic regimen, dietary precautions, adequate fluid intake, timely and correct administration of chemotherapeutic drugs form the main part of care. With subsequent cycles, the parameters are checked, side effects monitored and dose readjusted if required. After administration of chemotherapy the follow-up counts are done to monitor bone marrow depression and take remedial measures. During low counts precautions such as use of mask, hand washing, avoidance of exposed or uncooked food must be taken by patient to prevent infections. This forms the mainstay of **reverse barrier nursing**. **Barrier nursing** requires isolation of patients in a sterile atmosphere and the staff observes adequate precautions and is carried out in

special patients especially after BMT. Extravasation of the vesicant drugs is an emergency and tackled immediately.

Chemo-protectants: Side effects form a major problem of treatment and a concern for the patient as well as the clinician. To counter or prevent the side effects, several drugs are available. For control of emesis, combination of very effective anti-emetics is used including ondancetrone, dexamethasone. Other chemo-protective drugs available include granulocyte/granulocyte-macrophage colony stimulating factor (G-CSF/ GM-CSF) to prevent or treat neutropenia; amifostine to prevent systemic toxicity; dexrazoxane for cardiac toxicity. Mesna is used for prevention of hemorrhagic cystitis during ifosfamide therapy or high dose cyclophosphamide therapy. Most are available for routine clinical use in India and Armed Forces.

Regional chemotherapy: Apart from systemic administration, chemotherapy can be regionally administered by various routes, such as intra-thecal, intra-vesical, intra-arterial, intra-peritoneal or intra-pleural, for local control as systemic administration may not reach these sites in sufficient quantity.

High dose chemotherapy and BMT: Administration of high dose chemotherapy to eliminate the cancer cells almost completely is another strategy of cure. The principle is that of steep dose response curve, which means that higher the dose of the drug, higher is cell kill of the tumour and during this process, most of cancer cells are eliminated with a high dose of chemotherapy. As expected the normal cells are also damaged and especially bone marrow is permanently damaged and hence replacement of bone marrow is required for the survival of the patient. This forms the basis of bone marrow transplantation. The source can be related HLA matched (allogeneic), or patients' own bone marrow (autologous) or cord blood (obtained from cord blood of a newborn). Alternatively, circulating stem cells obtained from the peripheral blood after stimulation by G-CSF are the source of peripheral blood stem cell transplantation (PBSCT). Thus the haemopoietic transplantation is not a treatment by itself but a rescue to the permanent damage of the bone marrow by high dose chemo-radiotherapy employed to achieve a total cell kill. Sequence of events in this procedure are: bone marrow or stem cells are collected and stored at very low temperatures; the patient is administered chemotherapy and radiotherapy; bone marrow is infused to the patient; he is supported on blood component therapy in a protected environment till the engraftment, which takes about three to six weeks. Patient is discharged home within six to ten weeks.

Recent advances in chemotherapy: At present, there are many chemotherapeutic drugs and many more effective ones are being identified. New **differentiating agents** are available which lead to differentiation of a cancer cell into a normal cell rather than killing it. Example is all trans-retinoic acid (ATRA) used in treatment of pro-myelocytic leukemia. Drug resistance is a major factor limiting the response to the chemotherapeutic agents and to overcome the resistance new strategies are being worked out. A good venous access is a problem in patients receiving long-term chemotherapy and for

such patients several long-term venous accesses as Hickman's catheter or ports are available for ease of administration and convenience. Ambulatory infusion pumps have made it easy for the patient to have prolonged infusions with convenience without disturbance of their routine and at home. Drug administration has been under constant review with new concepts of dose intensity, dose density and chrono-chemotherapy.

Endocrine therapy inhibits the growth of hormone dependent tumour tissues and is mainly used in breast cancer (anti-estrogens), prostate cancer (anti-androgens). Tamoxifen is an anti-estrogen and is used extensively in breast cancer as an adjuvant therapy for prevention of systemic recurrences in estrogen receptor positive tumours as well as prevention of cancer in the opposite breast. Newer agents are also available at present in tamoxifen resistant cases. Flutamide is an anti-androgen and is used in treatment of carcinoma of prostate for treatment of systemic metastasis.

Immunotherapy of cancer is a new modality used in treatment of many cancers. The basis of treatment is that under normal circumstances there is immuno-surveillance, which prevents the carcinogenesis, and in immuno-deficiency states there is an increase in cancers. Classical examples are that of AIDS and post renal transplant patients, who have a higher incidence of cancers than normal population due to their immuno-deficient states. Immunotherapy aims at altering the immunity status of the patient to inhibit or eliminate the cancer cells. Several forms of immunotherapy are used including nonspecific and specific, active and passive strategies akin to immunization against infections. Levamisole is used as a non-specific immuno-stimulant in treatment of colo-rectal malignancies. Interleukins are used to activate normal T lymphocytes into lymphokine-activated killer cells (LAK cells) to kill cancer cells and this has been found to be useful in metastatic renal cell carcinoma. Interferon is used in treatment of chronic myeloid leukemia and multiple myeloma.

Genetic therapy is the most interesting of all the strategies as it attempts to correct the basic defect of cancer, hence may lead to real-cure of cancer in future. Replacement of defective genes, destroying the bad genes (oncogenes) or their products are some of the strategies. Monoclonal antibodies against several genes are available which can be used along with chemotherapy to treat breast cancer and low-grade lymphoma for better responses. With the completion of human genome project, more information and hence new therapeutic approaches will follow.

Role of Nurses: Oncology nurse forms a very important member of the multi-speciality team caring for the patient. In the modern practice, there are highly specialized oncology clinical nurses, research nurses and counselors. She participates in almost in every activity of the patient care, day-to-day management as well as research activity resulting in better patient care and contributes in a significant manner.

To conclude, medical management of cancers is comparatively new speciality and in last few years there have been many developments resulting in better responses, palliation and survival rates.