REVIEW OF LITERATURE
Cancer chemotherapy has its roots in World War I, when toxic effects of Mustard war gases over various systems especially over haematopoetic system (Spitz, 1948) were noticed when these gases were used as chemical weapons because of their varicant action on skin and mucous membranes. In 1918 at a base hospital in France, severe leukopenia was observed in patients nine days after they had been exposed to mustard gas (Krumbhaar, 1919). Eventually investigators recognised that these systemic effects might also reduce the number of malignant cells in certain cancers in particular, the leukaemia and lymphomas (Carter and Dershner, 1976).

In 1931 Adair and Bagg published the results of treatment with alcoholic solution of mustard gas (Di-chloro Di-ethyl sulphide). They referred to the observation of James Ewing and others on the destructive nature of burns caused by the gas and used it on tumours involving skin, it was applied topically in twelve cases and injected into the tumour in one, a recurrent neurogenic sarcoma. The tumours regressed and remission of a few months were obtained in other patients. Hopes were
expressed for the future use of mustard gas in cases of localised malignancies.

Chemically the nitrogen mustards differ from mustard war gases only in that a nitrogen replaces sulphur (Wintrobe, et al; 1947). In the early 1940's under the office of Scientific research and development with chemical warfare service of the United States Army, extensive investigation of the toxicology of nitrogen mustard were made (Burchenal, J.H. et al; 1948). In 1942 Goodmann and Gillman had studied the pharmacology of nitrogen mustard derivatives (Methyl chloro ethyl amine) and noted their effects on lymphoid tissues and dividing cells. The two compounds which received attention were known by the code name HN₂ and HN₃, the later trichlorotri-ethylene being the first to be used clinically (Goodmann et al; 1946). Clinical trials with HN₂, mustine Hydrochloride (Nitrogen mustard, Mechlorethamine hydrochloride), were initiated in 1943 in the united states and results were reported by RHOADS, 1946. Finally in 1945-46 during early clinical trials at an Army Hospital, Nitrogen mustard was demonstrated to be the first chemotherapeutic agent used, to successfully treat Hodgkin's disease (Cook, W.L., et al 1950). During the same time period, the antimetabolites were developed when the researchers
discovered that slight modification of the structure of Folic acid made it a growth arresting metabolic antagonist. Farber et al began clinical trials with Folic acid antagonist in 1940's and studied the effect of Folic acid metabolism on leukaemic cells resulted in the second cytotoxic drug of therapeutic value the anti-folate (antimetabolite) Methotrexate.

Thereafter many naturally occurring substances were listed for anti tumour activity in experimental models, many of them are in clinical use now.

**SCIENTIFIC BASIS OF CHEMOTHERAPY**

**QUANTITATIVE KINETIC APPROACH :**

Since in most instances qualitative metabolic differences between normal and neoplastic cells have not been discovered, the chemotherapist must plan according to quantitative differences in the proliferative kinetics of normal and Neoplastic cells growth of tumour regression without major host toxicity is to be achieved.

**THE CELL CYCLE :**

Through the use of radioactive labelling of the nitrogenous base, thymidine, in the early 1950's, it become apparent that DNA synthesis is not constant between periods of Mitosis, had been thought, but there
is a distinct gap in interphase both before and after the period of DNA formation. This information led to the development of the cell cycle model which comprises of the following stages:

M - Period of cell division.

G₁ - Postmitotic period, in proliferative cycle (RNA, and protein synthesis).

G₀ - Post mitotic period, temporarily out of proliferative cycle, "resting cells" - when stimulated, cells move into G₁ and begin to multiply again.

S - Period of DNA synthesis.

G₂ - Premitotic period (RNA and protein synthesis). For a given cell line 'S' (Synthetic phase), 'G₂' (Premitotic phase) and 'M' (Mitotic phase) are nearly constant, when 'G₂' phase is very long the cells can be considered to be in 'G' resting phase.

**CELL SPECIFICITY OF ANTINEOPLASTIC AGENTS**:

Chemotherapeutic agents may be classified into the three general types based on the stage of the cell cycle at which they exert their major effects.

**CELL CYCLE SPECIFIC AGENT**:

These agents exert their effects as long as the cells are dividing they are not cytotoxic to the cells.
in the resting 'G₀', stage but are toxic to cells in any other cell cycle stage.

**PHASE SPECIFIC AGENTS:**

These agents exert their effects only when the cells are in a specific phase (or stage) of the cell cycle. Some agents, such as the vinca alkaloids, are cytotoxic only when the cells are in the M-phase, while others whose principal action is inhibition of DNA synthesis, are toxic to cells only when they are in the S-phase. Hydroxy urea and cytosine arabinoside are in this category. Some agents are only relatively S-phase specific; this means that besides being able to inhibit DNA synthesis, they also can inhibit RNA and protein synthesis. The result is a slowing of the cell cycle with prevention of cells from entering the more sensitive S-phase. Methotrexate, 5FU, 6TG, and 6-MP appear to exert their effects in this manner.

**CELL CYCLE NONSPECIFIC AGENTS:**

Cell cycle nonspecific agents are effective when cells are dividing as well as when they are in the resting (G₀) stage these agents exert their effects directly on DNA, and therefore their activity is not enhanced by administering these drugs in the S-phase (Horton and Hill, 1977). Nitrogen mustard, dacarbazine, and mitomycin appear to be in this category (Baserga, 1965).
RATIONALE FOR CHEMOTHERAPY:

Regardless of whether the intent of chemotherapy is partial response and short term palliation, complete remission with prolonged survival, or cure, there are many principles that govern the use of cancer chemotherapeutic agents:

1. A single cancer cell is capable of proliferating exponentially to form a tumour mass, breaking away from the mass and travelling via the lymphatics and blood stream to other body sites where it can proliferate to form another tumour mass (metastatic disease). By this method it eventually can kill the host.

2. As a tumour mass increases, the time it takes the tumour to double in size, the "Doubling time" depends on three factors (March and Mitchell, 1974).
   (a) The time it takes a cell to complete one cycle of growth and division (its "generation time").
   (b) The fraction of cells undergoing division.
   (c) The tumour's "cell death" rate.

Because of the interplay of these factors it can not always be assumed that a small tumour is an early tumour (Silver et al, 1977).
3. Cure is accomplished only when the last cancer cell has been eradicated by surgery, by radiation therapy, or by chemotherapy - either alone or a combination of these - with or without the benefit of the host's own defense mechanisms.

4. Assuming that all kinetics, biochemical, and pharmacological factors are constant, most cancer chemotherapeutic agents in any given dose kill the same percentage, not the same number of cells. For example, if a chemotherapeutic agent with an 80% kill rate is administered into someone with a tumour consisting of one million cells, then after the first dose 800,000 cells are killed and 200,000 remain alive. Assuming there is no regrowth, after a second dose 160,000 are killed and 40,000 remain alive, and after a third dose 32,000 cells are killed and 8,000 remain, and so on. Thus, the same dose generally will kill the same percentage of cells regardless of whether the tumour is large or small. However, this is not strictly true, because of the variable number of cells in cycle as tumours size changes and because of poorly understood chemical changes and resistant subpopulations that emerge
during the course of chemotherapy.

5. Although chemotherapeutic agents are more toxic to malignant cells than to normal cells (called selective toxicity), the host's normal cells will experience some degree of injury. The rapidly renewing cell populations, such as those of the gastrointestinal (GI) tract, Bone marrow, and hair follicles are those that are most likely to be affected.

6. Benefits of treatment with chemotherapeutic agents must outweigh the side effects.

7. Antineoplastic agents are frequently given in an intermittent course of therapy (every 1 to 8 weeks) to allow restoration of the number of normal cells that were affected by chemotherapy. During this waiting time between treatments, the cancer cell population also increases but, with successful chemotherapy, remains smaller than what the population was prior to the initiation of chemotherapy. Successful chemotherapy (cure) implies reduction of the cancer cell population with each successive treatment. Chemotherapy is considered to be unsuccessful if, during this period of waiting for the patient's normal cells to recover from the
cytotoxic effects of the drugs, the tumour cell population recovers and grows to a number that is more than the starting number of cells. Survival time may be prolonged even though this occurs, but if there is a successive increase in cancer cell population with successive course of treatments, eventually a fatal number of cancer cells is reached and death occurs (Silver et al; 1977).

8. Cancer chemotherapy is most effective when the tumour burden is small (less than 10^9 tumour cells) and there is no clinical evidence of disease.

9. Some tumours produce biochemical markers that indicate the presence of disease when there is no clinical evidence of disease present. Examples are the production of abnormally high levels of human chorionic gonadotropin (HCG) in patients with choriocarcinoma and 5-hydroxyindoleacetic acid (5-HIAA) in patients with carcinoid tumours classification of chemotherapeutic agents.

**IN ANTI METABOLITE GROUP :**

Purine analogues as an anti metabolite was developed and the role of mercaptopurine as an antimetabolite was
shown by Burchenal and others in 1953. The Pyrimidine analogue fluoro-uracil (5-Fluoro-uracil) was used clinically in 1958 (Heidel berger et al; 1963) and later thio-guanine and others were tried and introduced into clinical use. Cytosine arabinoside was also shown to possess antitumour activity by Evans et al, 1961. A new fluorinated pyrimidine (Ftorafur) has been developed in the U.S.S.R. which has been extensively listed in Japan, and is now under evaluation in the U.S.A. (Blokhina et al; 1972).

- ALKYLATING AGENTS:

In this group Mustine and trichlorotritylamine were used parenterally (Goodmann et al, 1946, Rhoach, 1946). The first oral alkylating agent used clinically was tretamine (tri-ethylene – melamine, TEM) and a series of oral nitrogen mustard derivatives were synthesized at the Chester Beatty Research Institute London. Chlorambucil, Melphalan (Haddow and timmis, 1953) are still widely used. Thiotepa (triethylene thio-phosphoramide) was used as an adjuvant to mastectomy in a rational co-operative study under the direction of the National Institute of Health, with doctor Rudolf Noor as Chairman 1964.

ANTIBIOTICS:

Antibiotics were also being investigated for antitumour activity. Actinomycin D from a strain of Streptomycyes was shown to have antitumour activity in animals
(Schulte 1952; Waksman, 1960, Faber et al, 1960; Faber, 1966). Almost at the same time Mitomycin C was developed in Japan (Frank et al, 1960). Daunomycin (Daunorubicin) was studied by Di Marco et al, 1963. While Adriamycin was reported to have antitumour activity in Sarcoma by Bonnadonna et al; 1969. Later, Adriamycin was utilized for thyroid cancer (Gottlieb, 1972). Bleomycin has been used to successfully cure testicular tumours (Blum et al, 1973).

ALKALOIDS AND NITROSOUREAS:

These agents were of special interest to the scientists. Vincristine and Vinblastine were shown to be successful in treatment of Hodgkin's disease and other tumours by a number of workers (Holes et al, 1960; Johnson et al, 1960; Warwick et al, 1960). In 1972 a new plant alkaloid VM 26 (Citrovorum) was reported to be effective in lymphoma, glioblastoma (Sklansky et al, 1973) and intracerebral L1210 leukaemia (Muggia, et al, 1971). Among Nitrosoureas, carmustine (BCNU), Lomustine (CCNU) and Semustine (Methyl CCNU) have been shown to have variable response rate in advanced gastrointestinal cancer (Moertel, 1973), while streptozotocin is the only drug which has been meaningfully evaluated in carcinoma of Pancreas (Broder and Caster, 1973).
MISCELLANEOUS AGENTS:

Many miscellaneous agents have been shown to possess antitumour activity. OP'DD (Mitotane) is an established agent for adreno-cortical carcinoma (Bergenstal, et al, 1960). Hydroxy urea has a place in the treatment of chronic myelocytic leukaemia (Kennedy and Yarbro, 1966). Unique among Chemotherapeutic drugs is an enzyme L-asparaginase (Broome, 1968) useful in the treatment of acute lymphocytic leukaemia (Burchenal and karnofsky 1970; Cohen et al, 1976; Editorial, 1971). Hexamethylmelamine and Decarba- zine (DTIC) are of importance in having anti-tumour activity against ovarian carcinoma and malignant melanoma (Wilson, 1970; Luce et al 1970). Procarbazine, a methylhydrazine derivative, act like an alkylating agent and is used in leukaemia, Hodgkin's disease and brain tumours (Spiers, 1967; Vasantha et al, 1974): the ability of some platinum complexes to inhibit cell division led to their investigation as anticancer drugs by Rosenberg and others in 1985. Cis-platinum (Platinum diamminodichloride, cis-diammine platinum II) has been most extensively used, & is highly effective in testicular tumours and ovarian carcinoma (Gottlieb and Drewinko 1975; Hill and Baserga, 1975).
NEW DRUGS:

Dibromo mannitol and 5-azacytidine have been demonstrated useful in leukaemia (Cancellos, et al, 1975; Vogle 1975). The drugs in study for phase I and II would be the new active drugs of tomorrow.

In alkylating agents, Iphosphamide is a cyclophosphamide analogue under trial for ovarian cancer, breast cancer and lymphomas (Cohen, et al, 1973; Ahmann et al, 1974). Asaley, a derivative of Melphan (Phenylalalnine mustard) and calactitol, a derivative of dihalohexitol have shown response in lymphoma and breast carcinoma (Elson et al, 1968). Anti metabolites Baker's antifol, a triazine anti-
folate (Skeel et al 1974; Rodrigaez et al 1975), Cyclo-
cytidine (NSCI 45668) a synthetic analogue of cytosine arabino-
noride (HO et al, 1974, Chawla et al 1974) and Diglycoaldehyde, a product of purine nucleoside, inosine (Kaufman and Mittelman 1975) are under clinical trial for different malignancies. Antitumour antibiotics chromomycin and 
piperazinedione isolated from a culture of streptomyces are being clinically tested in Japan, South Africa and United States (Slavick and carter 1973; Kovach and Moertel 1973; Gottlieb et al 1975; Pratt et al 1975) Random synthe-
tics cytembena (NSC 104801) and Laetrite (Amygdalin) are under observation (Carter, 1976; Frytak et al 1975; Moertel et al 1982).
At present, there are around 40 effective anti-neoplastic drugs available. The quest for new cytotoxic drug continues with optimism and there is still greater potential for the better application of available agents.

COMBINATION CHEMOTHERAPY:

In 1964 the simultaneous use of vincristine methotrexate, murcaptopurine and Pn-dinisone, the so called VAMP regimen in acute lymphoblastic leukaemia of childhood led the way to combined chemotherapy in other forms of malignant disease (Freidreich et al, 1964; Henderson, 1967; Henderson 1969). By combination chemotherapy maximum therapeutic effects can be achieved without increasing unduly, undesirable side effects (Carter & Sober, 1974; De vita and Scheir, 1973; De Vita et al, 1975).

THE FIVE GENERAL PRINCIPLES GOVERNING THE USE OF COMBINATION CHEMOTHERAPY:

1. Each drug in the combination should have been demonstrated to have some activity on its own against the tumour type for which the combination is being used.

2. Drugs with a similar mechanism of action should not be combined.

3. As far as possible the major dose-limiting toxicity
of each drug should differ from that of the other component of the combination.

4. Since it is rarely possible to avoid some overlap in toxicity to host tissues, it is usually necessary to reduce the dose of each of the component drugs compared with the optimal dose which would be used if the drugs were prescribed individually.

5. There should be no known adverse interaction between the drugs (J.F. Smyth, 1984).

RATIONALE OF USING INTERMITTENT COMBINATION CHEMOTHERAPY:

This is based on the two groups of facts:

(i) Different constituents of combination chemotherapeutic agents.
- Have different biochemical sites for action in the cell.
- Attacking cells at different phase of growth cycle.
- Synchronize the active cell cycle.
- Empirically.

(Lawrence DR: and Bennett, PN: 1980).

(ii) When drugs are used together in full doses, intermittent treatment at intervals of 2–4 weeks rather than continuous daily administration has been employed. Such an approach has two theoretical advantages.
First is that if a treatment programme exert to selective killing effect on tumour tissues over normal bone marrow, an interval of about two weeks is usually sufficient to allow the recovery of bone marrow to pretreatment levels without allowing regrowth of tumours population to tumours population to base line levels.

The second advantage is that interval scheduling may permit the recovery of the host's immunological mechanisms -between cycles of chemotherapy. (De Vita, VT Jr, 1983).

In many situations, cytotoxic drugs are capable of reducing only a fraction of tumour mass, that is why chemotherapy is adjuvant to surgery and or radiation therapy to lessen the total tumour load. Amongst the first reports Mrazek et al (1959) showed the use of nitrogen mustard post operatively in colo-rectal carcinoma. Since then many institutes/workers have been continuously reporting successful use of adjuvant chemotherapy e.g. Noer (1961) for breast cancer; Longmira et al (1968) for gastric carcinoma, Holden et al (1970) for colorectal cancer.

Since 1971 multi modality treatment has advanced as much that even 100% cure has been achieved in some cases
like in GIT cancers, sarcoma, of paediatric age group, wilms tumour, Ovarian Carcinoma, Bronchogenic and Breast carcinoma.

Clinical trials have demonstrated that cancers can generally be grouped into categories according to the effectiveness of systemic treatment (Vincent, T., De Vita, 1984). Malignant diseases can be ranked into group comprising those for which chemotherapy contributes to cure, those for which effective control prolongs useful life and those for which benefit is less certain or unproven.

I. TUMOURS FOR WHICH CHEMOTHERAPY CAN BE CURATIVE:
   - Acute lymphoblastic leukaemia (childhood)
   - African Burkitt's lymphoma.
   - Hodgkin's disease.
   - Wilm's tumour.
   - Non-Hodgkin's lymphoma (Diffuse histiocytic and nodular mixed type).
   - Testicular carcinomas (Teratomas)
   - Ewing's sarcoma
   - Rhabdo myosarcoma
   - Chorio carcinoma

II. TUMOURS IN WHICH CHEMOTHERAPY PROLONGS LIFE. (RESPONSE RATE 50%)
   - Acute Leukaemia (adult)
- Breast carcinoma
- Chronic leukaemia
- Myeloma
- Ovarian carcinoma
- Small cell lung cancer
- Osteogenic sarcoma
- Non Hodgkin's lymphoma (lymphocytic type).

III TUMOURS IN WHICH CHEMOTHERAPY SOMETIMES PROLONGS LIFE (RESPONSE RATE 50%)
- Head and Neck tumours
- Gastro intestinal carcinomas
- Bladder carcinoma
- Hypernephroma
- Endometrial carcinoma
- Malignant Melanoma.

IV. TUMOURS WHICH ARE USUALLY REFRACTORY TO CURRENTLY AVAILABLE CHEMOTHERAPY.
- Carcinoma oesophagus
- Colo-rectal carcinoma
- Squamous cell lung carcinoma

Clinical experience with alpha interferon-26 has shown marked therapeutic activity in hairy cell leukaemia. Interferons also have potential role in combination with cytotoxic drugs for treatment of multiple myeloma, cutaneous
T cell lymphoma, chronic lymphocytic leukaemia and among solid tumours, viz, melanoma, renal carcinoma and ovarian carcinoma (Spiegel, 1986).

RECENT ADVANCES IN CANCER CHEMOTHERAPY:

The ability to induce complete remission in Adult Acute leukaemia has improved dramatically over the past two decades. In this reference high dose continuous infusion of cyclophosphamide, cytrabine, vincristine and prednisone demonstrate, promising efficacy with minimal toxicity in referactory Adult acute leukaemia (Guttrie, 1987).

In 1988 Lo Russo et al, showed in a trial study of ten year that a combination of 5 FU/cisplatin & Bleomycin is most effective in management of paranasal sinuse carcinoma.

The result of the study conducted by Koga et al, 1988 prophylactic therapy of peritoneal recurrence of gastric cancer by continuous hyperthemic peritoneal perfusion with Mitomycin 'C' is simple, safe & effective.

Use of combined peripheral and central chemoembolization of liver tumours improves the survival in patient with primary and secondary liver tumours (Shimamura et al, 1988).

Combination chemotherapy regimen consisting of
Adriamycin & Mitomycin 'C' is an effective regimen for treating patients of breast carcinoma, previously treated with CMF (Colozza et al, 1988).

Combined modality of treatment with infusion of 5 FU, Mitomycin 'C' and Radiation is an effective & well tolerated treatment for adenocarcinoma of oesophagus and gastrooesophageal junction in advanced cases (Coia et al, 1988).

The combination of 5 FU, Adriamycin and cisplatin is an active combination for the treatment of metastatic adrenal cortical carcinoma (Schlumberger et al, 1988).

Combined treatment for advanced oral cavity cancer by combination of Neomycin, Vincristine, Mitalactol, Prednisone, and Methotrexate with leucovorin rescue followed by surgery appears both safe an promising treatment (Olasz et al, 1988).

Adjuvent chemotherapy for low stage non seminomatous germ cell tumour of the testis with vascular invasion offers good results (Sanderman & Yang 1988).

Combination chemotherapy with cyclophosphamide, Adriamycin and vincristine is active in malignant thymoma
and myasthenia gravis (Kosmidis et al, 1988).

Combination of cisplatin & Mitoguazone for induction chemotherapy in advanced head and neck cancers, gives good results (Forastiere et al, 1988).

Platinum programme may provide useful palliation for selected patients suffering from neoplasms arising from salivary glands and contiguous structures in head and neck (Caregan et al, 1988).

Management of stage III primary breast cancer with primary chemotherapy, surgery & radiation therapy rendered most patients disease free & produced excellent local control rate (Hortobagyi et al, 1988).

High dose cyclophosphamide in treatment of refractory lymphomas and solid tumour malignancies may be given with acceptable toxicity in heavily pre treated patients (Collins et al, 1989).

Low dose cytosine Araabinoside may be worthy of trial in patients with secondary acute non lymphoblastic leukaemia and myelodisplastic syndrome with resistant cases (Kumar et al, 1989).

High dose cisplatin may benefit selected patients
with inoperable advanced head and neck tumours (Havlín et al, 1989).

The present gains are sufficiently promising that for a few tumours it may be possible with present knowledge, by the rational combination of several drugs, or of drugs concurrently with surgery and X-radiation, to expect more complete control over cancer. Yet the cancer therapy has still a very vast arena to be explored by mankind, for mankind in times to come.

--000--