MATERIAL AND METHOD
MATERIALS AND METHODS

In the present study, a concerted effort has been made to evaluate the role of chemotherapy in ninety patients, having various malignancies, who were thought to be candidates for chemotherapy and were admitted in M.L.B. Medical College Hospital, Jhansi.

SELECTION OF PATIENTS:

Criteria for selection of patients for inclusion in the study was objective. Patients suspected of having malignancy were admitted to hospital. They were subjected to thorough clinical examination including detailed history and physical examination. Relevant investigations were made to confirm the diagnosis, as well as for classification and staging of malignancy. In all cases diagnosis was confirmed by histopathological examination. Staging of the disease was done according to INM CLASSIFICATION. After the diagnosis and staging, patient was assessed for chemotherapy according to type and stage of malignancy and then trial of chemotherapy was begun. Those cases were selected for chemotherapy, who
either were found unfit for radiotherapy or surgery, due to extensive spread of the disease or where disease had recurred after radiotherapy or surgery.

**CLINICAL CLASSIFICATION AND STAGING** was done to plan treatment strategy and to evaluate prognosis. Standardized nomenclature given by UICC, known as the TNM system was used to know anatomic extent of disease.

- **T** - extent of primary tumour ($T_0$, $T_{1-4}$).
- **N** - condition of regional lymph nodes ($N_0$, $N_{1-4}$)
- **M** - Absence or presence of distant metastasis ($M_0$, $M_{1-4}$).

After arranging $T$, $N$ and $M$ categories (with degrees of extent), these were then grouped into four clinical stages (e.g. I to IV). Alternatively typical clinical staging was done as follows:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary tumour $(T)$</th>
<th>Regional Lymph nodes $(N)$</th>
<th>Distant Metastasis $(M)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Mobile (Operable)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>II.</td>
<td>Mobile (Operable)</td>
<td>Mobile (Operable)</td>
<td>None</td>
</tr>
<tr>
<td>III.</td>
<td>Fixed (unoperable)</td>
<td>Fixed (unoperable)</td>
<td>None</td>
</tr>
<tr>
<td>IV.</td>
<td>Any of above</td>
<td>Any of above</td>
<td>Present</td>
</tr>
</tbody>
</table>

Depending upon organ involved, type of malignancy and stage of malignancy, following groups of patients were made:
1. Lymphomas - A. Hodgkins
   B. Non-Hodgkins

2. Leukaemias - A. Acute - Lymphocytic ALL
   Myelocytic AML
   B. Chronic - Lymphocytic CLL
   Myelocytic CML

3. Carcinoma Breast

4. Gastro-intestinal carcinoma - A. Gastric carcinoma
   B. Colorectal carcinoma
   C. Pancreatic carcinoma
   D. Gall bladder and liver carcinoma.

5. Urogenital Carcinoma
   A. Ovarian carcinoma
   B. Testicular carcinoma - Seminoma
      Teratoma
   C. Renal carcinoma
   D. Prostatic carcinoma

6. Miscellaneous
   A. Lung cancer
   B. Head & Neck cancer.

SELECTION OF DRUGS/REGIMEN - There are different drugs and regimens described for various groups of malignancies in this study, a regimen was chosen after following consideration.
1. simplicity - Regimen with minimum number of drugs involved was chosen.
2. Availability of drugs - Drugs easily available locally were chosen.
3. Cost consideration - As the patients usually had spent a lot of money already in the treatment, many patients could not afford costly drugs. Therefore, regimen was chosen to give maximum benefit with alternate cheap drugs.
4. Side effects/Toxicity of drugs - Serious undesirable side effects were determining factors in the choice of a drug. For example, neuropathy caused by vincristine limited its use, especially in the older patients. Vinblastine was similar and could be used instead. Daunorubicin and Adriamycin were cardio toxic.
5. Route of Administration - The oral route was convenient but unsuitable when high doses were required. High dosage usually had an emetic effect hence a parenteral preparation was prepared when high dose were indicated. An oral drug could not be given to a patient who was vomiting, unconscious or dysphagic. When there was doubt about the patient's reliability in taking medication the intravenous route was better method of administration. Intravenous preparation could cause
a severe local inflammatory reaction if they leaked from the vein into the tissues. Pain and swelling could persist at the site for a couple of weeks and the vein itself became thrombosed.

6. Drug dosage and schedule - the treatment objective was to provide the patient with the maximum therapeutic benefit and the minimum amount of morbidity. The relationship between the desired and undesired effects of a drug was termed as its "therapeutic index". Drug dose was chosen within a narrow range because of the dose response relationship and the low therapeutic index for most anti-tumour drugs. Depending on tolerance, dose adjustment were made for subsequent course of chemotherapy.

7. Sensitivity and Resistance to Drugs - might be primary, (natural) acquired or developing during course of treatment. So history of previous drug treatment was taken to overcome sensitivity or resistance to drugs.

TREATMENT PROGRAMMES

1. SINGLE DRUG CHEMOTHERAPY -
Single drug was used alone when the disease was found sensitive to only one agent or its derivatives with little or no clinical sensitivity to other types of drugs. Single drug was also used alone when no extra
advantage with drug therapy was expected.

2. **MULTIDRUG/COMBINATION CHEMOTHERAPY**

Concurrent or sequential use of multiple drugs was made to achieve maximum therapeutic effect without increasing side effects. Drug combination was made with following criteria.

- Each drug should be active when used alone.
- Each drug should have different mode of action.
- Toxic side effects of each drug should differ.

Various regimens used for different malignancies are described ahead.

3. **MULTI MODALITY THERAPY (ADJUVENT CHEMOTHERAPY)**

Chemotherapy was used after primary resection to prevent the growth of sub clinical micro-metastasis or prior to local therapy with surgery to reduce a tumour bulk. So multi modal therapy was given by combining surgical and/or radio therapeutic approaches with chemotherapy.

Various drugs/regimens used for different malignancies are as follows :-

1. **CARCINOMA BREAST**

   A. For early Breast cancer (Adjuvant chemotherapy)
CMF Regimens

Cytoxan (Cyclophosphamide) 100 mg/m² oral days 1 to 14
Methotrexate 40 mg/m² I.V. day 1 & 8
Flurouracil 600 mg/m² I.V. day 1 and 8
Repeated after 4 weeks.
Such six cycles were given.

B. For Advanced Breast cancer -

(I) CMF Regimen

Cytoxan (Cyclophosphamide) 900 mg/m² I.V. day 1
Methotrexate 50 mg/m² I.V. day 1
Flurouracil 600 mg/m² I.V. day 1
Repeated after 3 weeks.
Such six cycles were given.

(II) Cooper's Regimen (CMFVP)

Cytoxan (Cyclophosphamide) 80 mg/m² oral daily
Methotrexate 20 mg/m² I.V. weekly
Flurouracil 500 mg/m² I.V. weekly
Vincristine 1.0 mg/m² I.V. weekly
Prednisone 30 mg/m² oral daily
(taken after 12 days)

Course was given for six weeks.

LYMPHOMAS -

A. Hodgkin's disease (Stage III and IV)
(i) **MOPP regimen**

Mustine HCl         6 mg/m² I.V. days 1 and 8
Oncovin (Vincristine) 1.4 mg/m² I.V. day 1 and 8
Procarbazine        100 mg/m² oral days 1 to 14
Prednisone          40 mg/m² oral days 1 to 14

Prednisone was given in Ist & 4th cycle only.
Treatment free interval 14 days (so one cycle was of 28 days).
Such six cycles were given.

(ii) **COPP Regimen**

Cyclophosphamide     600 mg/m² I.V. day 1 and 8
Oncovin (Vincristine) 1.4 mg/m² I.V. day 1 to 8
Procarbazine         100 mg/m² oral days 1 to 14
Prednisone           40 mg/m² oral days 1 to 14

Prednisone was given in Ist and 4th cycle only.
Treatment free interval 14 days (so one cycle was of 28 days).

B. **Non Hodgkin's lymphoma**

**CVP Regimen**

Cyclophosphamide     400 mg/m² oral days 1 to 5
Vincristine          1.4 mg/m² I.V. day 1 only
Prednisone           100 mg/m² oral days 1 to 5

One cycle consists of 21 days (so treatment free interval was of 16 days).
LEUKEMIA

A. Acute Myeloid leukemia (AML)

(I) For induction of remission

Cytosine arabinoside 100 mg/m² I.V. 24 hrs
during days 1 to 3
Vincristine 1.4 mg/m² day 1
Daunorubicin 60 mg/m² I.V. days 1 to 3
Cycle repeated after 2 - 4 weeks.

(II) For consolidation and maintenance of Remission

Cytosine arabinoside 100 mg/m² I.V. 24 hrs.
drip x 2 days.
Vincristine 1.4 mg/m² I.V. x 2 days
Daunorubicin 60 mg/m² I.V. x 2 days
Course was repeated every 8th week.

(III) For CNS involvement

Cytosine arabinoside 50 mg - Intrathecal
twice a week
Methotrexate 0.15 - 0.25 mg/kg -
Intrathecal twice a week
(8 mg/m²) max. dose
12.5 mg/m²
B. Acute Lymphocytic leukemia (ALL)

(1) **For induction of remission**

Vincristine 1.4 mg/m$^2$ I.V. weekly

Prednisone 40 mg/m$^2$ oral daily

Given for 4 - 6 weeks.

For patients not responding to above treatment, added also Daunorubicin 25 mg/m$^2$ I.V. weekly x 3 weeks.

(11) **For Maintenance of remission**

Methotrexate 25 mg/m$^2$ oral twice weekly

Mercaptopurine 50 mg/m$^2$ oral daily

Both are given for 3 months.

After every 3 months, vincristine and prednisone are given for two weeks in same dose and schedule as in Induction therapy.

Such cycles were given for at least 2 years.

(111) **For CNS involvement**

Prophylaxis methotrexate 12 mg/m$^2$ (Max. 15 mg)

\textit{intrathecal}

Preventive Methotrexate 12 mg/m$^2$ (Max. 15 mg)

\textit{intrathecal twice weekly for 3 - 5 doses.}
C. Chronic Myeloid leukemia (CML)

(1) **For induction of Remission**

Busulphan (Myleran) 4-8 mg oral daily:

Given usually for 3 - 6 weeks (Max. 12 weeks)

Till TLC is 20,000/cmm.

For refractory cases - add

Mercaptopurine 50 mg/day for 5 days every week.

Given for 4 - 6 weeks.

(11) **For Maintenance**

Busulphan 2-4 mg oral daily.

Till TLC comes to 10,000-12,000/cmm.

Treatment was stopped when TLC was below

10,000/cmm.

Therapy was resumed when TLC INCREASED ABOVE

15,000/cmm.

D. Chronic Lymphocytic Leukemia (CLL)

(i) **For induction of remission**

Chlorambucil 4-8 mg/day oral

Prednisolone 30-40 mg/day oral

Given for 6 weeks with adjustment of doses according to TLC report.

(11) **For Maintenance**

Chlorambucil 2-4 mg/day oral

Prednisolone 15-20 mg/day oral
Given for 3-6 months (Prednisone was stopped after total 12 weeks).

GASTRO-INTESTINAL CARCINOMA

A. Gastric Carcinoma

(i) **FAM Regimen**

- Fluorouracil 500 mg/m² I.V day, 1, 8, 21 and 28
- Adriamycin 30 mg/m² I.V. day, 1 and 21.
- Mitomycin C 10 mg/m² I.V. day, 1

Treatment free interval 4 weeks.

Such 6 cycles were given.

(ii) **FM Regimen**

- Fluorouracil 325 mg/m² I.V. days, 1 to 5
- Mitomycin C 1.5 mg/m² I.V. day 1

Treatment free interval 2 - 4 weeks

Course of six cycles

B. Colo-rectal carcinoma

Parenteral 5 FU 15-20 mg/kg I.V. once weekly

Oral - 5 FU 15 mg/kg daily for 6 days

Then 15 mg/kg once weekly.

C. Pancreatic carcinoma

(i) **SMF Regimen**

- Streptozotacin 1 mg/m² I.V. day 1, 8, 29, 36
- Mitomycin C 10 mg/m² I.V. day 1
Fluorouracil 500 mg/m² I.V. day 1, 8, 29, 36
Treatment free period 3 weeks (Duration of cycle 8 weeks).

(ii) FAM Regimen
Fluorouracil 600 mg/m² I.V. day 1, 8, 29, 36
Adriamycin 30 mg/m² I.V. day 1
Mitomycin C 10 mg/m² I.V. day 1, 8, 29, 36
Treatment free period 3 weeks (duration of cycle 8 weeks).

D. Gall Bladder and Liver
fluourouracil 600 mg/m² I.V. or oral for 5 days

URO-GENITAL CARCINOMA

A. Ovarian Carcinoma (Stage III & IV)

CMF Regimen
Cyclophosphamide 150 mg/m² oral day 1 to 14
Methotrexate 40 mg/m² I.V. day 1 & 8
fluorouracil 600 mg/m² I.V. day 1 & 8
Repeated every 4th week.

B. Testicular carcinoma

PVB Regimen
Cis platin 20 mg/m² I.V. day 1 to 5
Vincristine 6 mg/m² I.V. day 1 & 2
Bleomycin 15 mg/m² I.V. weekly
Repeated after 3 weeks.

C. Renal Carcinoma
Renal cell carcinoma (Hypernephromas)
(1) PROVERA (Medroxyprogesterone)
   200 - 800 mg oral daily
   400 - 800 mg I.M. monthly

(ii) Vinblastine 6 mg/m² I.V. once every two weeks
Wilms tumour (Nephroblastoma)
Actinomycin D 15 M gm/kg for 3-5 days
Repeated after 2 weeks.
Vincristine 1.5 mg/m² I.V. weekly
6 week course.

D. Prostatic carcinoma
(1) Diethylstilbestrol 5 mg/day 1-3 mg oral daily.
(11) Homovan (Fosfesterol) 0.5-1.0 gm I.V. daily x5 days
(iii) In hormonal refracting cases
Adriamycin 30 mg/m² I.V. day 1
Cyclophosphamide 100 mg/m² oral day 1 to 14

6. MISCELLANEOUS
A. Lung carcinoma
Small cell carcinoma
VAC Regimen
Vincristine 1.4 mg/m² I.V. day 1
Adriamycin 50 mg/m² I.V. day 1
Cyclophosphamide 750 mg/m² I.V. day 1

Repeated every 3 weeks.

B. Non small carcinoma

FAN Regimen

Fluorouracil 600 mg/m² I.V. day 1, 8, 29, 36
Adriamycin 30 mg/m² I.V. day 1
Mitomycin C 10 mg/m² I.V. day 1, 8, 29, 36

Treatment free period 3 weeks (Duration of cycle 8 weeks).

C. Head and Neck

(i) Methotrexate 50 mg/m² I.V. weekly
   Bleomycin 15 mg/m² I.V. weekly

   Course of 4-6 weeks.

(ii) Methotrexate 50 mg/m² I.V. weekly
     Vincristine 1.4 mg/m² I.V. weekly

     Course of 4-6 weeks.

FOLLOW UP AND SUPPORTIVE CARE

Patients coming for follow up of the therapy were subjected to following investigations specifically.

- Blood picture for pan-cytopaenia.
- TLC and DLC to exclude leucopaenia or Leucocytosis. Patients having TLC less than 3000/cmm were not given chemotherapy.

- Platelet count was done to see thrombocytopenia. Chemotherapy was given while maintaining count above 1,00,000/cmm.

- Haemoglobin to exclude anaemia with strong therapy. Support to the patient was given on the following aspects.

- Treatment of fluid & electrolyte balance.
- Prevention and treatment of infection.
- Treatment of Haemorrhage and anaemia.
- Psychological supports

EVALUATION OF TREATMENT

In order to evaluate response to treatment following observations were made at each consultation and cycle of therapy.

- change in size of tumour.
- change in size of liver, spleen and lymphnodes etc
- change in weight and appetite.
- Change in symptoms like pain, pallor etc.
- Performance status of patient.
CRITERIA FOR EVALUATION OF RESPONSE -

Three criteria of evaluation of response have been adopted.

1. Objective evaluation - was done in the following terms -
   (i) Complete response (CR). Complete disappearance of the known disease, determined by two observations not less than four weeks apart.
   (ii) Partial response (PR). 50% or more reduction in the sum of products of the longest perpendicular diameters of discrete measurable disease, with no new lesion appearing.
   (iii) No responses (NR): Less than 50% reduction or no change in the size of lesion or increase in the size of lesion or decrease in size of tumour less than 25%.
   (iv) Progressive disease: Appearance of any new lesion, or 25% or more increase in size of previous lesion.

Duration of response is the period which lasts from the date when response was first recorded to the date there after on which subsequent response is noted.

2. Subjective evaluation was done on following parameters (Performance status scale, ECOG).
0 - Able to carry on normal activity.
1 - able to live at home with tolerable symptoms.
2 - Disabling symptoms but 50% of time in bed.
3 - Severely disabled 50% of time in bed, but able to stand.
4 - Very ill, confined to bed
5 - Dead.

3. Evaluation of toxicity - was done in three categories:
   (i) Acute and sub-acute toxic effects-in which immediate (within seconds) and early (within hours) complications were observed.
   (ii) Chronic and late toxic effects-to observe intermediate (within days) and late (within months) complications.
   (iii) Death due to treatment.

PROCEDURES AFTER EVALUATION OF RESPONSE

On "Complete or partial response", the same chemotherapy, was continued.

On "No response" or "Progressive disease". the chemotherapy was altered in dose, schedule or components of regimen.

On toxicity, complications or side effects, the chemotherapy was either stopped or dosage were reduced or change in schedule or regimen was done with supportive care of patient.