SUPPORTIVE CARE IN ONCOLOGY : HISTORICAL PERSPECTIVES AND FUTURE OPTIONS

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Introduction

The recent advances in oncology have enabled us to cure approx. 50% of all individuals who develop cancer while the rest get varying degree of cure or may not get much in form of treatment, particularly when detected late in the course of illness. But all the patients irrespective of degree of cure require, at some or other time, relief from symptoms - both physical and emotional. The old proverb saying that *"it is duty of a physician to cure sometimes, to relieve often, to comfort always"* is most apt for an oncologist. An oncologist has to *"relieve often and to comfort always"* whether disease is curable or not[1]. So there is a need to take care of patient's physical, emotional and physiological reserves and **"Supportive Oncology"** has now developed as a well recognized discipline.

The term "Supportive Oncology" refers to those aspects of medical care that are concerned with physical, psychosocial, and spiritual issues faced by persons with cancer, their families, their communities as well as their health care providers. This includes both the adverse effects of antineoplastic therapies as well as "palliative" care. The term **"palliative"** means "to cloak or cover". The palliative care is concerned with providing maximum quality of life to these patients and their families.

The WHO definition of Palliative Care is[2]:

"The active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families. The palliative care may also be applicable earlier in the course of illness in conjunction with anti cancer treatment".

The Canadian Palliative Care Association (1995)[3] has modified and widened the WHO definition[3] and defines palliative care as "a combination of active and compassionate therapies intended to comfort and support individuals and families who are living with a life threatening disease". This should meet the physical, psychological, social and spiritual expectations and needs of patients. Palliative care may be combined with therapies aimed at reducing or curing the illness, or it may be the total focus of care.

Palliative medicine has also been described as an art and a science of patient - focussed, family - oriented, relationship - centered care, from the onset of a serious life threatening illness throughout the trajectory of illness, aimed at enhancing the quality of life and minimizing sufferings.

Thus the supportive care of the patient with any type of malignancy improves the quality of life as well as survival when combined with protocol based specific treatment. This improvement achieved is over and above the benefit anticipated from the specific therapy.

The supportive care involves the collaborative efforts of an inter-disciplinary team that includes patient, his/her family, care givers and involved health care providers. It is also necessary that care givers and health care provider's own emotions are also balanced in respect to care they are providing. The supportive care definitely includes focus on patient's common physical symptoms as pain, nausea, vomiting, weight loss etc. Supportive treatment modalities like blood component therapy, nutritional support, antimicrobial support and recent advances like growth factors, interferons, long term venous access and cytoprotection. The scope of supportive care extends to some issues related to medical ethics, survivorship issues, spiritual care, care of elderly, pediatric and AIDS patients. We shall be dealing with some of the important issues in detail.

A. CANCER PAIN : ASSESSMENT AND MANAGEMENT

Various studies have shown that around 30-60% of cancer patients experience pain during active therapy and more than two thirds of those with advanced disease get pain[4]. Pain is associated with heightened psychological distress and interferes with ability to eat,

sleep, think and interact with others. It may be incapacitating and preclude a satisfying quality of life.

The pain also provokes or exacerbates existing distress and contributes to a preoccupation with the mortality and outcome believes associated with malignancies. The treatment of pain is of utmost importance from all angles and clinician must maximize the knowledge, skill and diligence needed to attend to this task. The clinician tend to underrate the severity of pain as described by patient and hence the cancer pain remains undertreated most of times. Hence the assessment of pain must be optimal and discrepancies between patient description and physician assessment need to be minimised for its effective management.

The pain syndromes associated with cancer can be either acute or chronic. Whereas acute pains experienced by patients relate usually to diagnostic and therapeutic interventions, chronic pains are most commonly caused by direct tumor effects. Adverse consequences of cancer therapy (surgical, chemo or radiotherapy) account for 15-25% of chronic cancer pain problems[5].

The evaluation of pain characteristic are essential for use of proper therapeutic modalities and this evaluation should focus on intensity, quality, distribution and temporal relationship of pain. The evaluation of pain intensity is pivotal to therapeutic decision making. It indicates the urgency of pain relief, selection of drug, routes of administration and drug dosage etc. The quality of pain points towards its pathophysiology. Somatic pains are sharp aching, throbbing and well localized while visceral pains are generally diffuse and chronic ache type. Neuropathic pain may be burning, tingling or shock like. The distribution of pain such as focal, multifocal or generalized may be helpful in selection of therapy, such as nerve blocks, radiotherapy or surgical approaches. The sites of various referral pains must also be kept in mind. The pain may be associated with various other symptoms like moaning, grimacing, anxiety, tachycardia, palpitation or diaphoresis. Many a times pain may seem to be in excess of extent of identifiable organic pathology and not associated with predominant psychological symptoms. Such a pain be described as Idiopathic pain and be treated with suggestion in addition to drugs.

The pain assessment needs to be done with careful review of medical history followed by physical examination including a neurological evaluation. A review of previous laboratory and imaging studies is also important tool to point towards cause of pain and extent of underlying disease. The evaluation of pain should enable the clinician to appreciate the nature of pain, its impact and concurrent concerns that further undermine quality of life. Various tools used to rate the severity of pain are in use and include Memorial Pain Assessment Card (MPAC), Brief Pain Inventory (BPI) and Mc Gill pain Questionnaire (MPQ). The clinicians must also keep in the mind the transitory excerebration of severe pain over a baseline moderate pain, the so called "Breakthrough pains" that may be precipitated by volitional actions of patient such as movement, micturition, cough or defecation or by non volitional events such as bowl dysfunction[6]. These breakthrough pains must be differentiated from exacerbation of pain associated with failure of analgesia (End of dose failure).

It has been seen that 60-84% of cancer patients with solid tumours develop bone metastases[7] and this is seen more frequently with breast, prostrate cancer, multiple myeloma, lung, thyroid and kidney tumours. The most common presentation is a well localized dull ache that increases at night and by weight bearing. The commonest sites are pelvis, vertebrae, femur, ribs and skull. The other presentations include pathological fractures, loss of functioning and mobility, inadequate hemopoiesis, disruption of calcium haemostasis and spinal cord compression. The most widely used modality for detection of suspected bone metastases is radionucleotide bone scanning followed by MRI. The bone metastases also lead to pains - both chronic and acute. The pain intensity also varies widely amongst different group of patients depending on site of metastases.

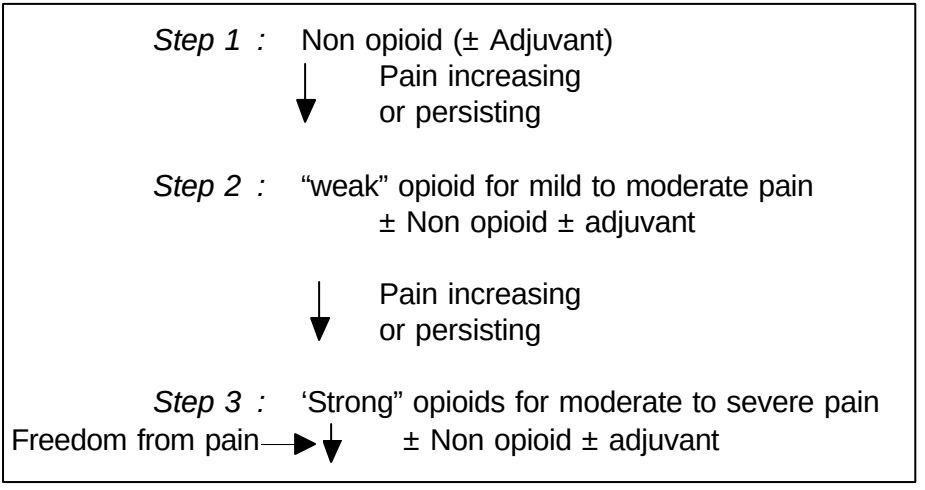
To summarize adequate assessment of pain characteristics is a necessary precondition for effective pain management.

Pharmacotherapy of Pain

There have been significant advances in management of pain associated with cancers but these remain underutilized due to poor physician assessment of severity of pain, inadequate knowledge of newer drugs & modalities and negative physician & patient attitudes towards use of opioids for pain[8].

After adequate pain assessment and evaluation on parameters described above, the pharmacotherapy must be individualized to maximize the pain relief and minimize adverse effects. WHO has devised a model paradigm for pain management approaches (Fig. 1).

Fig. 1 (WHO Analgesic Ladder)



The WHO approach advises the clinicians to match the patient's reported pain intensity with the potency of analgesic to be prescribed. For mild pain, one should use a *"non-opioid"* drug like acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) (Table I). For a moderate pain not controlled by NSAID alone, a *"weak"* opioid like codeine phosphate or hydrocodone bitartrate should be used in combination with aspirin, another NSAID or acetaminophen (Table II). For severe pain, a *"strong"* opioid such as morphine, hydromorphone, methadone or fentanyl should be used (Table II). The various pain management scales described earlier should be used to assess the outcome of pain management.

TABLE I: PARTIAL LIST OF ACETAMINOPHEN AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS USED FOR CANCER PAIN
(Adopted from Ref. 9)

Drug type	Typical starting dose
Acetaminophen	650 mg q4h p.o.
Aspirin	650 mg q4h p.o.
Ibuprofen	200-800 mg q6h p.o.
Diclofenac sodium	50-75 mg q8-12h p.o.
Flurbiprofen	200-300 mg q4-8h p.o.
Naproxen	250-750 mg q12h p.o.
Piroxicam	10-20 mg q daily p.o.
Ketoprofen	50 mg q6h p.o.
Ketorolac tromethamine	10 mg q4-6h p.o.
Ketorolac tromethamine	30 mg i.m. or i.v. x 1 then 15 mg i.m. or i.v. q6h

TABLE II: COMMONLY USED OPIOIDS FOR CANCER PAIN
(Adopted from Ref. 9)

World Health Organization step I/II opioids	Usual starting dose
Codeine phosphate	60 mg q3-4h p.o
Hydrocodone bitartrate	10 mg q3-4h p.o.
Oxycodone hydrochloride	10 mg q3-4h p.o.
Tramadol hydrochloride	50 mg four times daily p.o
World Health Organization step II/III opioids	
Morphine sulfate	
Immediate release	30 mg q3-4h p.o.
Also available as	10 mg q3-4h i.v.
Controlled and sustained release preparations	30 mg q12h p.o.
Morphine sulfate is also available as a suppository.	
Oxycodone hydrochloride	
Immediate release	10 mg q4h p.o.
Controlled release	20 mg q12th p.o.
Hydromorphone	6 mg q12h p.o.
Fentanyl	
Duragesic (transdermal)	50 mg/h q72h
Sublimaze via continuous infusion	50mg/h
Methadone hydrochloride	20 mg q6-8h p.o.
Levorphanol tartrate	mg q6-8h p.o.

The NSAIDs act by inhibiting enzyme cyclo-oxygenase, thereby inhabiting prostaglandin synthesis, which is an important mediator of inflammatory process. Recent introductions in NSAID therapy include two isoforms of enzyme cyclo-oxygenase, COX-I and COX-2. Ketoralac tromethadrine is available as oral, intramuscular and intravenous formulations. Various NSAIDs differ in their cost, dosing interval, analgesic ceiling and safety. The choice of NSAIDs must be individualized to patients need. The common adverse effects of NSAIDs include GI toxicity, ulceration and bleeding. NSAIDs and opioids have different mechanisms of action and logically would have additive analgesia.

The opioids form an essential component of pharmacotherapy of pain and can be classified as *"weak"* or *"strong"* depending on their relative efficacy in releasing pain (Table II). Morphine sulfate is the prototype opioid agonist and is designated by WHO, as *"drug of choice"* for treatment of severe pain associated with cancer. The half life of morphine is approx. 2 hours, and it is available both as oral immediate release preparation as well as slow release preparations that permit once or twice a day regimens. Oral administration of opioids is convenient, well tolerated, inexpensive and effective therapy. Morever these can also be used in epidural and intrathecal space in selected cases.

The most common adverse effect of opiates is constipation that may be result of reduced gastric, biliary, pancreatic and intestinal secretions and a decrease in propulsive motility of stomach and intestines. The other side effects include nausea and vomiting caused by direct stimulation of chemoreceptor trigger zone for emesis in medulla. Transient sedation is common when opioid therapy is initiated but it withers off with prolonged usage.

TABLE III: SIDE EFFECTS OF OPIOID ANALGESICS

Common	Uncommon
● Constipation	● Respiratory depression
● Nausea	● Seizures
● Vomiting	● Pruritus
● Sedation	● Xerostomia
● Mental clouding	● Myoclonus

The currently available pain management techniques make adequate pain control a realistic and achievable goal for virtually all patients with cancer. The adjuvant drugs used include certain anticonvulsants as gabapentin, carbamazepine and clonazepam; oral local anaesthetics, topical therapies, adrenergic receptor blockers like Clonidine and Tizanidine; N-Methyl -D- Aspartate Receptor antagonists like Ketamine, dextromethorphan and amantadine. Certain neuroleptics like fluphenazine and haloperidol are also being used increasingly for various neuropathic pains.

Some of commonly used non pharmacological therapies finding increasing acceptance in pain management include educating and reframing the patient and family needs, quick distraction and imagery, (hypnosis), music therapy, specialized Cognitive - Behavioural interventions. Some of the non pharmacological nociceptive modulation methods include massage, thermal modalities, therapeutic heat, hot packs, hydrotherapy, paraffin baths, radiant heat lamps, ultrasound therapies, therapeutic cold modalities, electrical stimulation etc. One may also choose to use equipments like various hand held stocks, walkers, wheel chairs and scooters. The restoration of normal biological alignment by straps, jackets, shoes, splints, and therapeutic exercises may also be helpful in management of pain of varying etiology and varying intensity.

Certain future neurosurgical interventions that may be helpful in pain management include medullary or pontine tractomy, medullary trigeminal tractomy, mesencephalotomy, thalamotomy, myelotomy and anterolateral cordotomy etc.

B. NAUSEA AND VOMITING

Nausea and vomiting in a patient with malignancy can be broadly of two types.

1. Chemotherapy related nausea and vomiting
2. Chronic nausea and vomiting

1. Chemotherapy related nausea and vomiting

This is one of the most feared effects of cancer treatment. Approximately 70-80% of all patients who receive chemotherapy experience nausea and vomiting[10]. Different chemotherapeutic agents

act at different sites to produce nausea and vomiting (Table IV).

TABLE IV: MECHANISMS OF NAUSEA AND VOMITING AFTER CHEMOTHERAPY (Adopted from Ref. 13)

- Stimulation of chemoreceptor trigger zone
- Peripheral mechanisms
  - Damage of gastrointestinal mucosa
  - Stimulation of gastrointestinal neurotransmitter receptors
- Cortical mechanisms
  - Direct cerebral activation
  - Indirect (psychogenic) mechanisms
- Vestibular mechanisms
- Alterations of taste and smell

It is important to note that a particular chemotherapeutic agent may produce nausea by acting through more than one mechanism, hence a single anti emetic regimen may not be effective all the time. Various chemotherapeutic agents have been classified into different levels depending on the frequency with which they cause vomiting [11]. These are classified as:

1) Level 1 < 10% frequency
2) Level 2 10-30% frequency
3) Level 3 30-60% frequency
4) Level 4 60-90% frequency
5) Level 5 > 90% frequency.

One may refer to this classification to know the level of nausea a particular agent can cause and institute necessary antiemetic measures when using these drugs accordingly.

A number of comorbid conditions that may lead to nausea and vomiting or aggravate nausea related to chemotherapy or radiotherapy are listed below in Table V.

TABLE V: COMORBID CONDITIONS THAT MAY LEAD TO NAUSEA AND VOMITING

- Central nervous system metastases
- Peritonitis
- Hepatic metastases
- Uremia
- Hypercalcemia
- Volume depletion
- Water intoxication
- Adrenocortical insufficiency
- Bowel
- Deficiency of specific nutrients
- Learned food aversion
- Taste and smell alterations
- Hunger satiety mechanisms
- Narcotics
- Psychological stress

The goals of antiemetic therapy for cancer patients on chemotherapy may be identified as follows.

1. To achieve complete control in all settings
2. To provide maximum convenience for patient and staff
3. To eliminate potential side effects of the agents.
4. To minimize the cost of treatment with antiemetic agents and drug administration.

The Phenothiazines were the main stay of anti-emetic therapy before the mid - 1970s[12]. In different studies in 1980s, patients ranked nausea and vomiting as first and second most severe side effects of chemotherapy. However with newer anti emetics agents and alterations in chemotherapeutic regimens, in an 1993 study, nausea was reported as most severe symptoms while vomiting was ranked fifth troublesome symptom. Therefore nausea is an important efficacy parameter when evaluating an anti emetic agent.

The commonly administered antiemetic agents are all 5-HT3 antagonists (Table VI)[13]. Even metoclopramide which acts through a dopamine receptor (O23) probably works via 5-HT3 pathway at higher doses.

Use of the newer antiemetic agents has decreased the incidence and severity of nausea and vomiting induced by chemotherapy. However these agents have not totally solved the problem. Adequate control of nausea and vomiting is a must to ensure patient compliance, follow up ultimately leading to a better quality of life.

TABLE VI: DOSES, SCHEDULES, AND CLASSES OF COMMONLY ADMINISTERED ANTIEMETICS
(Adopted from Ref. 13)

Antiemetic	Dosage
*** Serotonin receptor antagonists**	
Ondansetron	8 mg i.v. x 1 24 mg p.o. x 1
Granisetron	10 mg/kg i.v. x 1 2 mg p.o. x 1
Dolasetron	1.8 mg/kg i.v. x 1 200 mg p.o. x 1
Tropisetron	5 mg i.v. x 1
*** Substituted benzamide**	
Metoclopramide	1-3 mg/kg i.v. x every 3 h
*** Phenothiazine**	
Prochlorperazine	10-20 mg i.v. x 1 over 5 min
*** Butyrophenone**	
Haloperidol	1-3 mg i.v. q4-6h 1-2 mg p.o. q4-6h
*** Corticosteroid**	
Dexamethasone	10-20 mg i.v. x 1 over 5 min.
*** Cannabinoid**	
Dronabinol	2.5-5.0 mg p.o.q3-6h
*** Benzodiazepine**	
Lorazepam	0.5-2.0 mg i.v. q4-6h 0.5-1.0 mg p.o. 94-6h

2. Chronic Nausea and vomiting

The chronic nausea and vomiting are common and troublesome problems in patients with advanced cancer. It has been observed that nausea and vomiting developed in 62% of terminal cancer patients with prevalence rates of 40% in last 6 weeks of life with higher rates in women and younger patients[14].

Chronic nausea is presence of nausea for more than 1 week in absence of a well identified, self limiting cause. It is often multifactorial and requires long term treatment. The common causes of chronic nausea are:

1. Delayed chemotherapy induced emesis
2. Radiation therapy.
3. Opioids
4. Other drugs like antibiotics, NSAIDs
5. Anxiety
6. Increased intracranial pressure
7. Autonomic dysfunction
8. Bowel obstruction, constipation
9. Metabolic abnormalities
10. Peptic ulcer disease.

Before proceeding for management of chronic nausea, it is of utmost importance to carry out an assessment in a given patient as these symptoms are dynamic processes and frequently change in intensity. There are a number of effective scales to measure intensity of nausea such as visual analog scales, numerical scales and verbal descriptors but there is no "gold standard" for nausea assessment. The expression of nausea varies from patient to patient and will depend on individual patient's perception and his psychosocial state. A detailed history and examination is essential. It should also be clarified as how much nausea and vomiting interfere with oral intake and the patient's hydration status should also be observed. A history of early satiety or syncopal attack should raise suspicion about possibility of autonomic insufficiency.

All investigations to exclude renal impairment, hepatic failure and other metabolic abnormalities need to be done including metastatic profile, if indicated.

Management

Management includes general support measures such as maintenance of good oral hygiene, attention to diet and hydration and comfortable environment for patient. The specific treatment can be instituted in cases where a cause or metabolic abnormality has been detected after examination or investigation. The symptomatic treatment involves a number of pharmacological agents available. These are summarized in Table VII listing both currently available and future agents.

TABLE VII: ESTABLISHED AND EMERGING AGENTS FOR THE TREATMENT OF NAUSEA
(Adopted from Ref. 13)

Agent	Effects
Dopamine antagonists central action (e.g. metoclopramide, butyrophenones, phenothiazines)	Block dopamine at chemoreceptor trigger zone.
Dopamine antagonists peripheral action (e.g. metoclopramide, domperidone)	Promotility effects on gastrointestinal tract.
Antihistamines (e.g. Cyclizine, Promethazine, dimenhydrinate) **Corticosteroids** (e.g. dexamethasone)	Effects on vomiting center and vestibular apparatus. Reduce raised intracranial pressure. Also improve sensationof well being and appetite.
5-HT3 antagonists (e.g. ondansetron, granisetron)	Block 5-HT3 (serotonin), used in chemotherapy induced and postoperative vomiting.
Progestational agents (e.g. megestrol acetate)	Unknown, improve appetite, caloric intake, and nutritional variables in cancer cachexia.
Thalidomide	Centrally acting antiemetic effect. Other effects on improving appetite and sensation of well-being.
Cannabinoids Neurokinin 1 antagonists (not yet licenced) Octreotide	Central effects, antagonize substance P. Central effects,
Anticholinergic agents, e.g., hyoscine Butylbromide	Reduced gastrointestinal secretions in patients with inoperable bowel obstruction.
	Reduced gastrointestinal secretions in patients with inoperable bowel obstruction

5HT3, 5-hydroxytryptamine type 3.

Some cases may require surgical interventions in form of correction of intestinal obstruction, percutaneous gastrotomy, bypass procedures etc.

However, as on date, there is not significant research on the issue of chronic nausea and its management. Drugs that have been found to be effective in acute vomiting such as 5-HT3 and neurokinin-

1-receptor antagonists, require further evaluation in advanced cancer patients with chronic nausea.

C. NEUTROPENIAS AND ANTIMICROBIAL SUPPORT

In oncological practice, a significant fever is defined are a single reading more than 38.5^{O}C or three readings (at least an hour apart) of more than 38^{O}C. A Fever of Unknown Origin (FUO) is defined as an illness lasting at least 3 weeks with a fever higher than 38^{O}C on more than one occasion and which lacks a definitive diagnosis after 1 week of evaluation in a hospital[15].

Etiology of Fever in Cancer patients

Fever is commonly seen in cancer patients, both in those with or without infection. The common etiologies are:

a) **Tumor :** The tumors commonly associated with fever include Hodgkin's disease, lymphoma, leukemias, renal cell carcinoma, myxoma and osteogenic sarcoma.

b) **Infections** (including the neutropenia) **:** The fever and infection can be common presentation in cancer patients but it is of particular concern in neutropenic patients. Neutropenia (peripheral blood neutrophil count <500/l results either from increased destruction or decreased production of WBCs. The latter can be due to marrow involvement by disease or due to myelosuppression from chemotherapy. The cause of fever may not be identifiable in 60-70% of neutropenic patients[16]. However most febrile neutropenic episodes are assumed to represent infection as fever and neutropenia in cancer patients are associated with high risk of complications with a death rate ranging from 4-12%. It was also observed that mucositis was associated with decreased risk of complications, suggesting that infections associated with mucositis may be more responsive to antibiotics..

The organisms associated with infection have been changing over the years. Gram negative organisms were the leading causes of infection in febrile neutropenic patients but their incidence has decreased from 71% during 1973-78 period to 31% during 1989-91 period. The incidence of pseudomonas aeroginosa infection, one of commonest organism has also decreased over the years[17]. The incidence of gram positive organisms has increased from 29% during

1973-78 period to 69% during 1989-91 period. The incidence of both acute and chronic fungal infections has also increased. It is seen that upto 33% of febrile neutropenic patients not responding to a week of antibiotic therapy are having a systemic fungal (Candida or Aspergillosis) infection[18]. The common site of infection in neutropenic patients is gastrointestinal system (diarrhoea, odynophagia, gingivitis, bacterial peritonitis) followed by central nervous system, site of recent surgery, site of access lines in body, catheter sites etc.

In most of instances the available diagnostic tests are not sufficiently sensitive or rapid enough to identify causative organism, hence empiric antibiotic therapy is of utmost importance in these patients. This is discussed later in chapter.

c) **Transfusion related causes** like allergic reactions, infection transmission through blood particularly platelet concentrate are also causes of fever seen in cancer patients.

d) **Thrombosis** like deep vein thrombosis, pelvic thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral venous thrombosis may also be associated with fever.

e) **Haemorrhage** from GI tract may also be associated with fever.

f) **Drugs** like cytotoxic agents (Bleomycin, Cisplatin, Cytarabine, Cyclophosphamide, Methotrexate, Vinblastine, Vincristine), antibiotics (Penicillin, Cephalosporins, Amphotericin B), opioids (morphine, pethidine, drug withdrawal) and biological agents like Interferon, G-CSF (Granulocyte colony stimulating factors), GM-CSF administration may be associated with significant fever.

g) **Other causes** of fever may be Graft-vs-host disease, radiation induced fever, coexisting conditions like SLE, rheumatoid arthritis.

Management of Febrile Neutropenia

The treatment of fever in a non neutropenic oncology patient is not in itself an emergency but in a immunocompromised patient is a medical emergency and empirical therapy must be initiated as soon as possible. An overall scheme for neutropenic patients with fever is presented in Fig. 2.

The Infections Disease Society of America (ISDA) has come out with a consensus statement on use of antibiotics in patients with

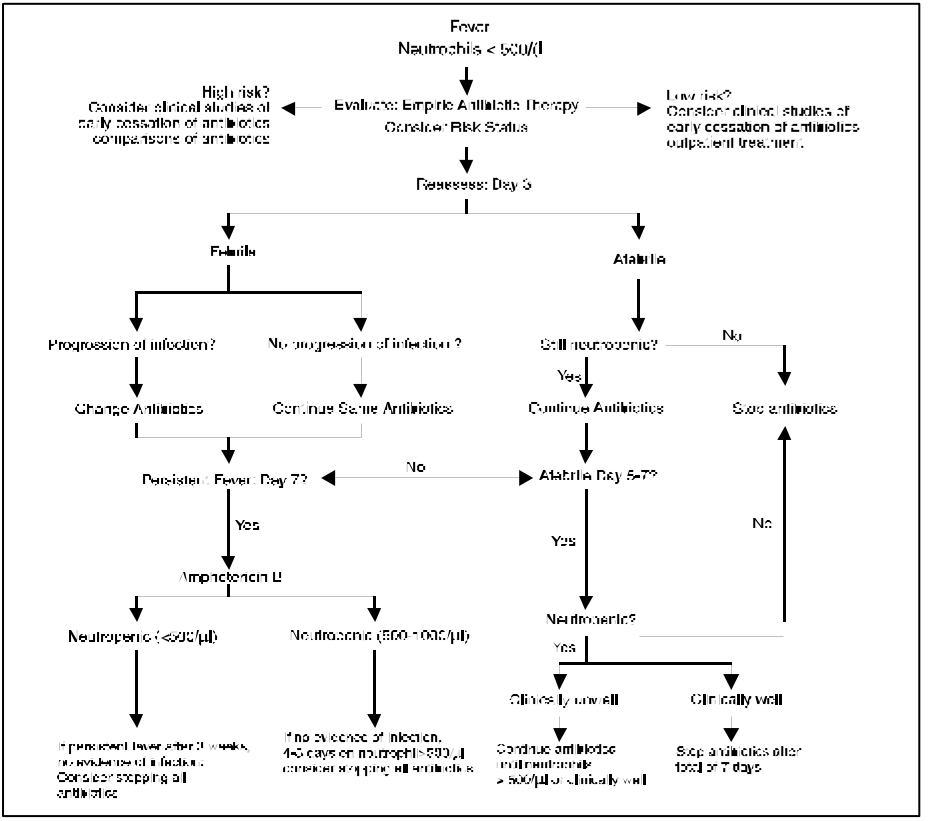


Fig. 2: Clinical approach to the treatment of patients with febrile neutropenia.

Febrile Neutropenia[19]. The therapeutic options available are: monotherapy, two drug therapy and vancomycin plus one or two other drugs. Ceftazidime and Imipenem - cilastatin are the most extensively studied drugs in of the monotherapy regimens, but cefepime and meropenem also appear have equal efficacy.

The most commonly used combination regimens are an aminoglycoside (gentamicin or amikacin) and an antipseudomonal penicillin (piperacillin, ticarcillin, clavulanate) or an aminoglycoside plus a third generation antipseudomonal cephalosporin (ceftazidime or cefepime). Combination regimens have synergistic activity against some gram-negative bacilli and gram-positive cocci and the dosage needed are lower and risk of emergence of resistance strains is reduced. The disadvantages of combination regimens are largely

attributed to the nephrotoxicity and ototoxicity associated with aminoglycosides.

The increased frequency of infection caused by gram positive organisms has led to widespread use of empiric vancomycin in cancer patients. Although empiric vancomycin showed superior initial rates of defervescence (76% vs 63% p <0.001) but it did not show any difference in infection related mortality (6% vs 7%) as subsequent vancomycin addition effectively managed drug failures. Furthermore, the overuse of vancomycin may be associated with the emergence of resistant strains[20].

If fever persists for more than 5-7 days, addition of amphotericin B is recommended. Upto one-third of patients with febrile neutropenia unresponsive to broad-spectrum antibacterial therapy have fungal infections like candidiasis and aspergillosis. Amphotericin B is administered in doses 0.7-1.5 mg/kg/day. In disseminated candidiasis, fluconazole is as effective and significantly less toxic as compared to amphotericin[21]. The antifungal treatment must be continued until all signs and symptoms of infection are resolved and for a minimum of two weeks. A number of lipid based amphotericin preparations have been introduced : amphotericin B colloidal dispersion (Amphotec), amphotericin B lipid complex (Abelcet) and liposomal amphotericin B (Ambisome). All are less nephrotoxic than standard amphotericin B deoxycholate preparation and of the three, liposomal amphotericin B appears to be associated with less infusion - related toxicity, but none are more effective than standard amphotericin preparation. The cost is increased significantly with these newer preparations.

In severe aspergillosis the overall success rate with amphotericin B is 34% and similar results are attained with itraconazole. The recommended dose of Itraconazole is 200mg orally thrice a day for 4 days then 200mg twice a day. Even after a course of “induction therapy” with amphotericin B “consolidation therapy” with itraconazole is often appropriate and rewarding.

Prophylaxis for febrile Neutropenia

a) **Growth factors :** Haematological colony stimulating factors (CSF) reduce treatment associated myelosuppression by shortening the duration of neutropenia and by reducing the nadir of neutrophil counts.

The guideline for use of CSF have been revised by American Society of Clinical Oncology[22]. It has been observed that benefit of CSF in primary prevention varies from type of cancer to type of chemotherapy used. Its use is advocated only in those protocols where incidence of febrile neutropenia is likely to greater than 40% without their use. When less myelotoxic chemotherapy is planned, primary use of CSF should be reserved for only high risk patients.

If a patient has already experienced chemotherapy induced neutropenia, than CSF can be used if there is a proven benefit in maintaining the dose. The secondary use of CSF has a definite benefit in reducing the infection associated mortality. Two main types of CSF in use are i) Granulocyte macrophage colony stimulating factor (GM-CSF) for use in patients with mucositis and infection; ii) Granulocyte colony stimulating factor (G-CSF) for prophylaxis of febrile neutropenia as well as for reconstitution of stem cells in high dose chemotherapy. The recommended dose is 5 μg/kg for G-CSF (and 250 $\mu g/m^2$/day for GM-CSF) administered 24-72 after chemotherapy until the neutrophil count is greater than 10,000/μl after the neutrophil nadir. Though these agents are expensive but the cost of their administration may be balanced by lower hospital expenses due to shorter stay in hospital and lower usage of drugs and laboratory.

The four main types in usage are:

1) Fligrastem (E.coli derived G-CSF)
2) Sargramostim (yeast derived GM-CSF)
3) Molgramostim (E.coli derived GM-CSF)
4) Second Generation Growth factor (under evaluation)

The doses of G-CSF and GM-CSF are 5 μg/kg/dais and 250 μg/m2/day respectively and their usage guidelines are given by American Society of Oncology in Table VIII[23].

TABLE VIII: AMERICAN SOCIETY OF CLINICAL ONCOLOGY GUIDELINE HIGHLIGHTS

FOR COLONY-STIMULATING FACTOR (CSF) USE
(Adopted from Ref. 23).

- **Primary prophylactic** use should be reserved for those patients with expected incidence of febrile neutropenia of >40%. Primary prophylaxis should not be used in most patients receiving most standard chemotherapy regimens.
- **Special populations.** Certain populations that are at higher risk for infections complications because of bone marrow compromise or other complications may be considered for primary prophylaxis.
- **Secondary prophylactic use.** Dose reduction can be considered rather than CSF use in those with previous febrile neutropenia or prolonged neutropenia.
- **Treatment:** CSFs should not be used to treat afebrile neutropenia or in cases of uncomplicated febrile neutropenia. Those high-risk patients with profound neutropenia, sepsis, or documented infection may benefit from adjuvant treatment with CSFs.
- **Acute myeloid leukemia**: CSFs can be used to decrease the duration of neutropenia following induction chemotherapy and possibly following consolidation.
- **Radiation:** CSF use should be avoided in those receiving concomitant chemotherapy and radiation.

b) Other prophylactic measures

The Infectious Diseases Consensus Panel has recommended trimethoprim - sulfamethoxazole prophylaxis for afebrile, uninfected patients with profound neutropenia expected to persist for atleast 1 week. Similarly Ciprofloxacin has also been found to be effective in reducing incidence of fever complicating neutropenia during therapy. However it should be given only to neutropenic patients. Antiviral prophylaxis with acyclovir also reduces chances of herpetic gingivostomatitis (and CMV pneumonitis) in patients with neutropenia.

D. NUTRITIONAL SUPPORT

The patients with malignancy have highest prevalence of malnutrition among any hospitalized group of patients (other than AIDS now). In its most severe form, weight loss due to malignancy is termed the *"Anorexia - Cachexia Syndrome"* and is characterized by anorexia, skeletal muscle atrophy, tissue wasting and organ dysfunction[24]. Malnutrition associated with malignancy is a poor prognostic indicator and is associated with higher morbidity and mortality rates.

The potential causes of malnutrition in cancer patients include direct and indirect effects of tumour such as change in taste, dysphagia, pain, GI obstruction and early satiety as well as due to antineoplastic therapy in form of chemotherapy & radiotherapy, anorexia, nausea, mucosal ulcerations or infections. Also the patients with various malignancies may have altered metabolism of nutrients and significant amount of calories may be lost in futile pathways leading to major losses in both total weight and lean body mass over the long term.

Adunctive nutritional support

The goal of nutritional care in cancer patients should always be considered supportive whether the aim of primary therapy is cure or palliation. Nutritional therapy should be aimed at improving metabolic status, body composition, functional status and ultimately, quality of life. A nutritional support in form of either total parenteral nutrition (TPN) or external feeding is desirable in patients on antineoplastic therapy but these are not indicated for patients with advanced metastatic disease who are not receiving antineoplastic therapy. The motto of therapy is "If the gut works, use it", so if a person can tolerate enteral nutrition, there is no role for TPN. Some studies have reported decreased post operative complications and decreased mortality in patients receiving TPN as compared with enterally fed patients of GI carcinoma. But recent studies have shown no beneficial evidence of TPN in patients undergoing chemotherapy or radiation therapy. However two recent studies have shown increased survival (in patients of bone marrow transplantation) who received TPN as compared to controls [25]. The beneficial effect may be due to controls having oesophagitis and enteritis, resulting in severe nutritional depletion. There was an initial

enthusiasm in providing glutamine enriched TPN to cancer patient in decreasing bacterial translocation and bacteremia. But this has still not been proved in placebo controlled studies.

The various assessment tools to see the nutritional status are body mass index, rate weight loss, serum albumin, anthropometrics like Triceps circumference and arm muscle circumference, biochemical indicators like BUN, creatine height index, catabolic index, serum transferrin levels and albumin levels.

The caloric requirements are calculated according to BMR (Basal metabolic requirements) calculated by Harris - Benedict equations. The daily lipid requirement is 0.5-1 gm/kg/day while protein requirements are 1.5-2 gm/kg based on ideal body weight. The fluid intake is calculated as per baseline requirements, daily losses, environment and fluid deficits. It varies from 1250-3000 ml/day. The electrolytes are included in all parenteral nutrition solutions. If the GI tract is intact and functioning, liquid formula diets are preferred. Oral supplements help to bolster up the caloric and protein supply. However patients often suffer from anorexia, nausea, oropharyngeal obstruction, or CNS pathology and may require feeding nasogastric tubes - may be intermittent, bolus, pumped or simple continuous feeding tubes. It has also been seen that parenteral nutrition administered alongwith insulin are helpful in improving skeletal muscle protein synthesis and whole body protein net balance. Addition of glutamine to standard TPN solutions has been done for long time but recent studies have not shown significantly better results in terms of rate of infection or hospitalization.

Immunonutrition in cancer patients (Therapy of future)

Recently certain substances have been shown to enhance or preserve host immune responses and/or to reduce harmful and exaggerated inflammatory responses. This approach of adding such substances (like arginine, omega 3 fatty acids, nucleic acids and glutamine) is termed as Immunonutrition[26].

Arginine improves macrophage tumor cytotoxic effects, bactericidal activity and vasodilation through production of nitric oxide; stimulates T cell proliferation and generation of lymphokine - activated killer cells and modulates nitrogen balance and protein synthesis.

Omega-3-fatty acids are potent anti inflammatory agents and upregulate the immune response. Glutamine reduces intestinal and skeletal protein waste during stress, enhances macrophage phagocytosis and preserves the intestinal permeability.

Probiotic bacteria such as lactobacillus not only preserve key nutrients but also increase its content during storage conditions.

Recently many studies have compared immune enhanced diet (IED) with standard enhancing diet (SED) and found significant reduction in overall combined infections and wound complications in the former group.

To conclude, it is very important to prevent malnutrition and cachexia in cancer patients as far as possible. The enteral route is always preferable to TPN in terms of physiological response, immunocomplexes, quality of life and cost. The concept of immunonutrition is catching up fast and is a thing of near future.

E. HAEMATOLOGIC SUPPORT

Cytopenias are a frequent and sometimes dangerous complication of malignancy and its treatment. The causes are quite varied and difficult to establish. Earlier we used to have only transfusion products and time as the tools to fight them but now we have some valuable additions to our tools that are quite effective, though expensive at present.

Anaemia

More than 50% of all cancer patients are anaemic regardless of treatment received and approx. 20% of all patient undergoing chemotherapy will require RBC transfusion during their treatment course. Patients with lung cancer, lymphoma, genitourinary tumors and gynaecological malignancies have the highest transfusion rates. Anemia within haematological malignancies is always seen.

The etiology of anaemia is multifactorial and is consequence of disease as well as its treatment. Erythropoietin plays a key role in RBC production and in anaemia due to cancer. It acts by stimulating the burst forming units - erythroid (BFU-E) and colony forming units - erythroid (CFU-E). Malignancy can affect erythropoietin functioning by decreasing marrow responsiveness to it or by decreasing

erythropoietin production, as tumour necrosis factor and some nephrotoxic agents can. So erythropoietin supplementation becomes crucial in treatment of anaemia of malignancy. The debate about level of anemia requiring transfusion continues. The concept has been that acute anaemias always require blood transfusions while in chronic anaemias, various compensatory mechanisms come into play, plasma volume is compensated, cardiac output is maintained and they do not need blood transfusion. However there is new evidence that all cancer patients, even those with chronic anaemia, benefit significantly from haemoglobin levels near normal, hence the role of transfusions in such patients needs to be rediscussed.

Novel Erythropoiesis - Stimulating Protein (NESP) (darbopoietin alpha) is an erythropoietin analogue with increased glycosylation and a bigger molecule. Its half life is greater in i/v as well as S/C dosages and it can given at weekly intervals.

Neutropenia

It is one of most common, dose limiting toxicity of chemotherapy regimens. About 10% of neutropenic patients may have fever and mortality due to neutropenia may be as high as 3%. Neutropenia with or without fever has already been discussed in detail earlier in this chapter alongwith different type of growth factors.

Thrombocytopenia

The complications due to thrombocytopenia vary from harmless echymoses and petechiae to disruptive epistaxis and gingival bleeds, to life threatening gastrointestinal and intracranial haemorrhages.

The treatment of thrombocytopenia is still the same : prevent or treat the haemorrhage by supplementing the platelet levels. The prophylactic platelet transfusions are common, frequent and are standard of care in oncology patient. However the threshold at which platelet transfusion must be given has been changed from 20,000/µl in the year 1992 to 10,000/µl in the year 2000. The guidelines for platelet transfusion are summarized in Table IX[27].

TABLE IX: AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE

GUIDELINES FOR PLATELET TRANSFUSIONS (Adopted from Ref. 27).

- 10,000/μl should be the prophylactic threshold for adult patients with adult leukemia and most solid tumors.
- 20,000/μl should be considered for some tumors that, due to tumor necrosis, are particularly at risk for bleeding. Examples include melanoma, bladder, gynecological, and colorectal tumors.
- Platelet counts greater than 50,000/μl should be reached before surgery.
- To reduce alloimmunization, leukoreduced blood products should be used in patients who will require continued platelet transfusions.
- Patients refractory to platelet transfusions should be treated with HLA-matched platelets.

The platelet support in thrombocytopenic patients can also be achieved by use of recombinant human Interleukin II. This was first cytokine apprised by VS FDA to stimulate platelet production[28]. Certain other agents under development are PMP (Promegapoietin) and MGDF (megakaryocyte growth and development factor). It has been observed that thrombopoietin (TPO) induces proliferation of megakaryocyte progenitor cells, expansion of megakaryocyte in vivo and production and release of platelets.

F. ISSUES IN PALLIATIVE CARE

Although palliative care is a part of broader term *"Supportive Oncology"*, it is beyond the scope of present chapter. It involves discussion on various models of palliative care, hospice care, communication at end of life, palliative chemo/radio/surgical therapies. The issues of home care, symptoms of an actively dying patient, spirituality, bereavement care, staff care and burnout are some of common issues in palliative care. We also need to form guidelines on palliative care and Physician Assisted Death, ethics and law in this regard. The Rehabilitative therapy, long term survivorship issues and palliative care in HIV/AIDS patient and ICU settings are some of other contentious issues.

For routine and emergency haematological and other malignancies, it is important to have long term venous access for patients with malignancy. There are two types of venous access systems:

1) Peripherally introduced Central Catheter (PICC)
2) Centrally inserted catheters (CIC)

The PICC utilizes one of superficial veins like veins in arm or leg while CIC uses subclavian or internal jugular veins.

Both these catheters may have external access available or implanted part system which are placed subcutaneously.

PICC lines are indicated for short duration therapy (upto 6 months), for low volume injuries and single or sequential chemotherapeutic agents. The problems involved are occlusion (requiring weekly flushing) and phlebitis, maintenance is difficult, patients daily activities are limited. In case of implantable ports, patients activity is not affected, maintenance is easy, infection rates are low and longevity of device is better. However these are expensive and difficult to place.

CIC lines with external access are easy to use, can be used for large volumes of fluids, also for blood sampling and multiple drug infusions are possible.

The catheter infection can occur in catheter, at exist site, tunnel or pocket. The incidence of late catheter thrombosis is quite high.

G. ALTERNATIVE MEDICINE

A lot of stress is being laid these days on alternative therapies and recently music and art therapy have been used in pain management with very good results.

The Music and Art therapies are non pharmacological therapies offering a range of calming and expressive benefits to patients and their families. Music therapy has been used to alter mood, promote relaxation, improve communication and break the cyclical nature of pain[29]. Theoretical models and methods of treatment have been developed and are being used by music therapists in area of pain management, music and neurological sciences, psychotherapy and integrative medicine.

The Complementary and Alternative Medicine (CAM) is a broad term comprising a vast collection of disparate approaches, from unproved cancer cures to soothing, adjunctive regimens (30). Alternative regimens are usually invasive and biologically active. These are usually expensive and potentially harmful. They may harm directly through physiological activity or indirectly when patient postpones receipt of mainstream care. Complementary therapies are used for symptom management and to enhance well being. They serve as adjuncts to main stream care to enhance patients quality of life. Some of commonly used therapies are metabolic therapies and detoxification, megavitamin and orthomolecular therapy, mind - body techniques, bioelectro magnetics, immuno augmentative therapies (IAT), manual healing methods, therapeutic touch (TT), herbal remedies, message therapy and acupuncture. Some of other therapies in this group are spiritual care, counselling and group support. Our challenge in CAM is to help patient avoid the pitfalls of useless unproved therapies, while ensuring their access to safe, non invasive, beneficial complementary modalities available.

CONCLUSION

The goal of good supportive care is not only to relieve sufferings but to improve quality of life also. Hence the supportive care should start as soon as a diagnosis of cancer is made and should continue through out the treatment and palliative care should be used only for end of life/terminal stages. The various components like pain management, nausea and vomiting management, nutritional support, haematological support, antimicrobial therapy and various growth factors are all utilized to give a longer and better life to patients. The treatment related toxicities should be minimized and treated whenever they occur.

Cancer, despite all advances, has a devastating effect on patient, their families, community and health care providers. The provision of a excellent supportive care is extremely rewarding for patients and satisfying for the health care provider.

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