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Challenges of cancer staging and therapy in critically ill patients

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ABSTRACT

The number of patients diagnosed with malignancy has increased significantly with the advent of new diagnostic modalities, so has the overall prognosis with the dawn of new therapeutic interventions. However many of these patients require critical care admissions as an aftermath of cancer or its treatment. There still exists a dilemma as to which cancer patients to admit and when to admit. The purpose of this review is therefore to outline principles of critical care in cancer patients with special emphasis on critical and palliative care as well as appraisal of economic and ethical aspects in their management.

Key words: Cancer, Critical Care, Intensive Care Unit (ICU), Prognostic Factors

INTRODUCTION

Cancer, a major health hazard has skyrocketed in the recent years. According to estimates there are expected to be 15 million new cases of cancer by 2020¹. Increase in life expectancy, behavioral and lifestyle changes, improved cancer diagnostic and therapeutic modalities have all led to this surge. As per the Indian Council of Medical Research (ICMR) projections, there will be over 17.3 lakh new cases of cancer and over 8.8 lakh cancer related deaths with cancers of breast, lung and cervix topping the list. Breast cancer in females and oral cancers in males are the major killers. Ironically the overall prognosis of many solid tumors and hematological malignancies has improved significantly due to early detection, management and better ICU triage of cancer patients². Many cancer patients may require ICU admissions due to metastatic organ damage, associated infections due to immunotherapy or chemotherapy, electrolyte imbalances like hypercalcaemia, hemorrhagic and thrombotic predisposition and need for mechanical ventilation in the setting of acute respiratory distress syndrome (ARDS), thereby highlighting the pivotal role of the intensivist in conjunction with the oncologists in managing these patients^{3,4}.

PURPOSE OF THIS REVIEW

The notion that cancer is catastrophic, not requiring ICU admission, though unjustified still prevails. Conversely there are many chronic illnesses which though non malignant carry gloomy prognosis. ICU admissions in cancer patients predominantly involve those undergoing surgical interventions or victims of therapeutic interventions. The purpose of this review is to highlight the principles of ICU care and illustrate the important role of the intensivist in the management of cancer patients as also the challenges faced in the therapeutic interventions of cancers in ICU.

INTENSIVE CARE OF ICU PATIENTS: WHEN TO ADMIT?

Intensive care units are continuously flooded with critically ill patients creating a dearth of available ICU beds.

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Therefore admission of a cancer patient in ICU requires a careful triage to impart maximum benefit to the cancer patients. The purpose of intensive care is to optimize these patients rather than treat the underlying pathology. These triage decisions involve a multidisciplinary team comprising of intensivists and medical and surgical oncologists, psychologists, nurses and palliative care and ethics specialists. The usual scoring systems i.e., Acute Physiology and Chronic Health Evaluation (APACHE) II or III, Simplified Acute Physiology Score (SAPS II) or mortality probability models (MPM II) cannot be implemented on critically ill cancer patients^{5,6}. Moreover the various cancer triage scoring systems that have been devised are of no use to the intensivist as they are common to both the medical and surgical oncology with varied prognosis^{7,8}. Moreover with the advent of therapeutic innovations cancer prognostic factors which were previously given lot of importance are of no significance.

CANCER PROGNOSTIC FACTORS

Neutropenia

Neutropenia in cancer patients previously associated with poor outcome due to secondary infections has no longer prognostic significance⁹.

Hematopoietic stem cell transplantation

Allogenic Hematopoietic Stem Cell Transplantation (HSCT) when associated with complications like acute lung injury or acute respiratory distress syndrome ALI/ARDS, pneumonias, graft versus host disease, haemorrhage necessitates ICU admission in 16%-40% patients, with mortality rates up to 42%-88%. However use of autologous HSCT, colony stimulating factors for neutropenia as well as administration of steroids and early use of non invasive ventilation has improved the prognosis^{10,11}.

Age

Age per se cannot be considered as an independent prognostic tool though in patients >60 years with concurrent critical illnesses and multiorgan failure have grave prognosis¹².

Type of underlying malignancy

Hematological tumors though previously thought to fare poorer than solid tumors, have a better prognosis now with novel therapeutic advancements¹³.

Stage of malignancy

Patients with advanced malignancies or those associated with metastasis have poor ICU outcome.

Cancer related complications

Acute complications related to cancer often necessitate ICU admission, the incidence being 5% in patients with solid tumors and 15% in those with hematological malignancies¹⁴. These include tumor lysis syndrome, secondary infections as a sequelae to chemotherapy or immunotherapy, hyperleukocytosis, organ dysfunctions, sepsis and respiratory distress. Moreover certain moribund patients are more prone to thrombotic microangiopathies, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), electrolyte aberrations like hypercalcemia or haemorrhagic or thrombotic manifestations¹⁵. Similarly cancer relapses and recurrences have poor prognosis. Infact a relapsed/treatment unresponsive leukemia is a poor prognostic factor in acute leukemias^{12,16}. Incidence of acute renal shut down is 12%–16% and is a consequence of tumor itself or drug related toxicity, the incidence being more with haematological than solid tumors^{17,18}. Similarly neurological complications in the form of seizures, confusion or coma are the result of malignant infiltration by cancer cells, infection or Posterior Reversible Encephalopathy Syndrome (PRES)^{19,20}.

Complications of cancer therapy

Secondary infections resulting from neutropenia due to cancer chemotherapy is one of the important indicators of ICU admission. Infact the risk of sepsis is 15 times than that of general population with every 10th patient dying as a result of this. The risk is 9 times more in haematological malignancies than the solid tumors²¹. Drug induced organ failure, anaphylaxis and cytokine release syndrome are other cancer therapy related adverse events which require ICU care.

Patient performance status

Performance status prior to hospitalization is a pivotal prognostic tool, a poor status associated with increased mortality in moribund cancer patients²².

Comorbidities

Cancer patients with coexistent comorbidities like diabetes, hypertension, chronic obstructive pulmonary disease, not only have deleterious outcomes but also increased risk of therapy related complications^{23,24}.

Palliative critical care of cancer patients

Many a times ICU admissions in incurable cancer patients are indicated for palliative care in the form of sedation for intractable pain. Similarly short term ICU stay may be required for revertible complications like tamponade or need for non invasive ventilation during respiratory compromise in otherwise non curable tumors.

MANAGEMENT OF CRITICALLY ILL CANCER PATIENTS

Management of critically ill cancer patient requires a collaboration of intensivist and medical and surgical oncologist.

- Respiratory distress:** One of the major criteria for the ICU admission of cancer patient is the presence of respiratory insufficiency or failure. These patients can be managed by Non Invasive (NIV) or invasive ventilation. Early institution of NIV is the cornerstone of management especially so in patients with isolated respiratory failure due to cardiogenic pulmonary oedema or hypercapnic respiratory failure in COPD. A 15% mortality has been reported in patients in whom NIV is initiated early without a subsequent need of invasive ventilation in contrast to an alarming 95% mortality seen with late incitation of NIV compared to 78% in patients who were intubated in first place²⁵. Invasive ventilation is indicated in case of NIV failure due to delay in its initiation, development of ARDS or need for renal replacement therapy and vasopressors²⁶⁻²⁸. Use of humidified high flow nasal cannula is another way of managing respiratory distress²⁹.
- Infection and sepsis:** Chemotherapy triggered neutropenia or myelosuppression by malignant infiltration as well as immunosuppression due to treatment are the main culprits of infection and sepsis. Polymicrobial infestations are common necessitating the need for broad spectrum antibiotics.
- Cancer chemotherapy:** In critically ill cancer patients, dose adjustments of chemotherapy are required in the setting of organ failure, dialysis or Extra Corporeal Membrane Oxygenation (ECMO). Moreover interactions with concomitantly administered drugs have also to be looked into. Prior to administration of drug therapy in these moribund patients, risk and benefits have to be weighed, as hastened mortality may be seen on administration of antineoplastic therapy in organ dysfunction. Coexisting infection is not a contraindication to chemotherapy but in the setting of severe organ dysfunction particularly respiratory insufficiency one may need to ponder³⁰.
- Adverse drug reactions:** Antineoplastic therapy is associated with side effects majority of which are mild to moderate. (Table 1) But in one third cases catastrophic events can occur requiring critical care

attention³¹. Their management requires a thorough knowhow of drug mechanism. These unpropitious events are more common in the presence of organ dysfunction³¹. These effects can be both on target or off target. These manifestations can be in the form of hypertension, gastrointestinal bleeding or perforation, thromboembolic events, neurotoxicity, hepatotoxicity, colitis, pleural and pericardial effusions etc. Of particular relevance is the Cytokine Release Syndrome (CRS), the deleterious outcome of immunotherapy. It is caused by a fatal surge in inflammatory mediators interleukin-6 and interferon-gamma which incites a systemic inflammatory response³². Symptomatology includes fever with chills, hypotension, tachycardia during or immediately after drug administration mimicking anaphylaxis. Oliguria, bronchospasm, dyspnea, confusion, urticaria are other manifestations³³.

Table 1: Showing adverse reactions of new anticancer drugs

CLASSIFICATION	ADVERSE REACTIONS
MONOCLONAL ANTIBODIES Rituximab Ofatumumab Obinutuzumab Trastuzumab Cetuximab Bevacizumab	CRS, Immunodeficiency, Diarrhea, Exanthem, Gastrointestinal bleed/ Perforation.
TYROSINE KINASE INHIBITORS Imatinib Dasatinib Ponatinib Idelalisib	Pleural/ Pericardial effusions, Thromboembolism, Diarrhoea.
BISPECIFIC ANTIBODIES (BAB) Blinatumomab	CRS, Neurotoxicity and Hepatotoxicity
CHECKPOINT INHIBITORS Ipilimumab Nivolumab	Diarrhoea , Colitis, Immunohepatitis Polyarthritis
CELLULAR TREATMENTS Chimeric antigen receptor T cells	CRS, Neurotoxicity

*CRS- Cytokine release syndrome

- Cardiopulmonary Resuscitation (CPR) in cancer patients:** CPR in cancer patients has poorer outcome as compared to other patients^{34,35}. Moreover patients with advanced malignancies in hospital CPR is usually futile and those who make it have a poor quality of and short survival time.³⁶ However recent studies have shown a higher survival rates probably because they do not include "Do Not attempt Resuscitation" (DNR) patients of cancers who are terminally ill^{36,37}. Acute renal failure, shock unresponsive to treatment, patients on invasive mechanical ventilation, prolonged CPR are all negative predictors of CPR^{36,38}.

End of Life Care (EOLC) in ICU

A patient in ICU needs to be periodically evaluated and sometimes crucial End of Life Care (EOLC) decisions need to be taken. These decisions are joint ones involving not only the critical care specialists and the oncologists but also the preferences of the patients and their kiths have to be looked into. EOLC involves the termination of life prolonging interventions with emphasis on palliative care. These include Do Not Resuscitate (DNR) and withdrawal of all the life support with death ensuing within few hours after withdrawal³⁹. However in India there are many legal implications in implementing EOLC with issues on euthanasia still unclear⁴⁰. EOLC decisions on cancer patients are based on patients and their families preferences, patients quality of life, prognosis and cancer triage.

Ethical issues in critical cancer care

Cancer care is fraught with many ethical issues. Divulging the cancer and its outcomes has always been an ethical dispute Inclusion of these patients in clinical trials for new therapeutic interventions is an ethical challenge. Maintaining patients and their families' autonomy in decision making is of utmost importance especially when withdrawal from active support and end of life care decisions are to be addressed.

Social, behavioral and economic and aspects of cancer

Cancer is an expensive ailment to treat particularly in developing nations where because of limited access to health insurance abandonment of treatment is common. This is especially so in families where the sufferer is the main bread earner and the rest of the family struggles to pay for the expenses. This also holds true if the mother is affected because her children will be devoid of care. Poverty coupled with ignorance leads to adoption of traditional therapies leading to delay in treatment and putting considerable financial debt on these families.

Costs of cancer care are estimated to escalate in the near future due to innovations in cancer therapy⁴¹. Infact increasing cost will be an important determinant in decision making process by intensivists and oncologists.

FUTURE OF CRITICAL CANCER CARE

With the advent of less invasive life support techniques and advancements in medical and surgical management of cancer patients, the overall prognosis has improved significantly thereby escalating the number of patients qualifying for intensive care admissions putting a higher burden on the developing than on developed nations^{42,43}. Therefore extensive researches are required to delineate guidelines for ICU admissions of cancer patients for a better triage. Prospective studies appraising the needs of moribund cancer

patients are the need of the hour⁴⁴. Studies targeting on the long term outcome of cancer patients with emphasis on the satisfaction of family as well as the quality of life after ICU/hospital discharge need to be devised⁴³. Novel approaches need to be formulated to improve the quality of life in cancer patients with imminent death. Future progress in the critical care cancer management requires the development of comprehensive cancer centers to deliver high-quality evidence based treatment options to these patients.

CONCLUSION

With novel diagnostic and therapeutic interventions the overall prognosis of cancer patients has improved tremendously. Infact critical care should be incorporated early in cancer management to reap maximum outcomes in those who can benefit and to provide optimal palliative care in terminally ill. This requires a multidisciplinary approach involving critical care specialist, medical and surgical oncologist as well as palliative care specialist. Due consideration should be given to the ethical and social and economical aspects of critical care. This will culminate to delivery of high quality critical care to cancer patients.

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