Mechanical Ventilation in Critically Ill Cancer Patient

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11.1 Introduction

Respiratory support in cancer patients can be very challenging and tricky. Irrespective of underlying acute pulmonary pathology, it depends on many other factors such as severity of underlying malignancy, ongoing treatment and/or further treatment plan, any treatment related cardiorespiratory dysfunction and its reversibility, current immune status and anticipated duration of immuno-suppressive state (if any), intent of therapy and anticipated life expectancy, wish of the patient and the family members and financial burden related to advance organ support. Invasive respiratory support like mechanical ventilation needs to be used judiciously, especially in the background of advanced pulmonary malignancy, metastatic disease, severe immunocompromised state and palliative intent of therapy. If the patients do not have enough reversible factors, they may be dependent on invasive respiratory support for prolonged duration without significant improvement in final outcome. On the contrary, not offering mechanical ventilation just because of underlying malignancy is also not a right clinical decision. So clear understanding of the cause of respiratory failure and current status of malignancy along with vision about long term outcome and expectation of the family members will guide us to take correct decision in terms of respiratory support.

a. Respiratory support strategies:

In past, respiratory failure in cancer patients used to have poor outcome. Presently because of advancement of cancer therapy, the anticipated life span of patients has been prolonged. Up to 20% admission of mixed medical-surgical ICU have underlying malignancy [1]. Respiratory failure is the most common cause of ICU admission along with major cause of death in this sub-group of patients [2]. Respiratory

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V. Kumar et al. (eds.), *Onco-critical Care*,
https://doi.org/10.1007/978-981-16-9929-0_11

failure can be related to malignancy (cancer related or chemo-radiotherapy related) or unrelated to it (decompensation of co-morbidities, pulmonary infection or other infection). It can be classified as acute, sub-acute and chronic (depending on onset of the disease) or type 1 to type 4 (pathophysiological classification). Type of respiratory support is decided based on pathophysiological changes in pulmonary system. Detailed clinical and radiological assessment will guide to identify the level and extent of pathology to airway (upper and lower), alveoli, interstitium, pulmonary circulation; or extra-pulmonary causes like pleural space, thoracic wall, diaphragm and accessory muscles; or systemic causes like cardiovascular, renal or central nervous system.

b. Non-invasive ventilation (NIV):

Historically, mechanical ventilation in cancer patients specially with haematological malignancy and post bone marrow transplant, had very poor outcome with high mortality rate. As invasive ventilation bypasses the upper airway immune protection, chance of micro-aspiration along the cuff of endotracheal tube (ETT) leading to ventilator associated pneumonia (VAP) is very high. Studies have shown that prevalence of silent aspiration of gastric contents in mechanically ventilated patients, confirmed by pepsin measurement in bronchoalveolar lavage (BAL), can be as high as 89% [3]. Additionally, there can be bleeding or bacterial transmigration through the eroded mucosa by ETT cuff. Recently significant improvement has been achieved in the outcome of cancer patients requiring mechanical ventilation, even for the patients with haematological malignancy. Therefore, avoiding invasive ventilation is not a current norm in cancer patients.

European Respiratory Society/American Thoracic Society (ERS/ATS) clinical practice guideline for use of NIV in acute respiratory failure has recommended NIV in indications like acute exacerbation of COPD with respiratory acidosis, cardiogenic pulmonary oedema, immunocompromised patients, palliative care patients, post-operative respiratory failure, chest trauma and prophylactic usage for weaning from mechanical ventilation [4]. But data for hypoxaemic respiratory failure due to pulmonary pathology is not available to make any recommendation, especially for de novo lung pathology. In most of the immunocompromised patient, the sub-group comprising of haematological malignancy and post bone marrow or solid organ transplant patients, NIV has been compared with supplemental oxygen [5–7]. Results are little heterogenous in terms of need for mechanical ventilation and mortality; even then it is difficult to extrapolate the positive outcomes in other subgroup of cancer patients.

Empirical NIV usage for all cancer patients admitted in ICU with acute respiratory failure may lead to high failure rate. Multifocal pulmonary infection/Acute respiratory Distress Syndrome (ARDS), progressive disease, newly diagnosed lung cancer, associated other organ failure, high disease severity score, male sex, prolonged NIV, high respiratory rate, NIV as first line therapy for respiratory failure and septic shock/concomitant use of vasoactive agents are main negative predictive risk factors [8, 9]. Hypoxaemic respiratory failure de novo is not immediately reversible and need prolonged respiratory support to reduce the work of breathing. High metabolic demand in sepsis leads to high inspiratory flow requirement.

Combination of large intra-pleural pressure swing because of spontaneous breathing effort with high inspiratory pressure in NIV lead to high and variable transpulmonary pressure and tidal volume, which may worsen early lung injury—self inflicting lung injury (SILI). High inspiratory pressure in NIV may lead to poor toleration, leak, gastric distension and aspiration [10, 11].

High Flow Nasal Cannula (HFNC)—HFNC can be an interesting modality for acute respiratory failure in cancer patients—specially with type 1 failure. It is a simple machine capable of delivering warm (37 °C) and humidified oxygen up to a flow rate of 60 l/min. It consists of oxygen compressor, specialised flowmeter capable of 60 l/min flow, humidifier, corrugated heated tube and nasal cannula at patient end. Along with delivery of high FiO_2, it also decreases dead space, develops certain amount of positive end-expiratory pressure (PEEP) (2–7 cm H_2O depending on flow rate and whether mouth is open or close) and improves patient's compliance. It has been used with good effect in cancer patients under palliative care [11]. But role of HFNC in cancer patients with acute respiratory failure need further evaluation.

In last decade, HFNC has been used extensively in hypoxaemic respiratory failure in general population. Frat et al. [12] in FLORALI trial, have compared HFNC with supplemental oxygen and NIV in ARDS patients. Even though the intubation rate is same, 90-days mortality was less with HFNC compared to the others. But study on immunocompromised patients [13] has shown that HFNC decreases intubation rate but does not affect mortality. So, if used judiciously, HFNC is non inferior to supplemental oxygen and NIV as per current literature.

The usage of NIV for acute respiratory failure has increased significantly over last 2 decades [14]. Even though the evidence is lacking, the use of NIV is significantly more for hypoxaemic respiratory failure (non-COPD) than patients with hypercarbic respiratory failure (COPD). Non—COPD patients have higher chance of NIV failure requiring invasive ventilation. Patients with failed NIV trial usually have poor outcome [15, 16], which may be due to delayed intubation/failure to pick up right time for invasive ventilation leading to progressive pulmonary damage due to volutrauma and barotrauma followed by emergency intubation because of rapid deterioration. So, patients having risk factors for NIV failure need more intense monitoring of their respiratory parameters.

There are different predictive scoring systems for anticipating NIV failure. Commonly used score is HACOR score [17]. HACOR score is an objective scoring system that comprises of heart rate, acidosis, consciousness, oxygenation, and respiratory rate. Maximum score is 25. Score more than 5 at 1 h of NIV trial predicts high chance of NIV failure (87%) and also mortality (65%), specifically if intubation is delayed more than 12 h. So, use of NIV should be conducted with strict monitoring of the objective criteria for identification of NIV failure to avoid undue delay in intervention such as invasive ventilation.

c. Invasive ventilation- Conventional & Non-conventional modes of ventilation (Biphasic- Bilevel, APRV, high frequency ventilation)

Proper selection of patients and improved critical care management have resulted into improved outcome of cancer patients requiring invasive ventilation. There are two challenges related to this—difficult airway & ventilatory strategies.

Airway: Airway management always requires special mention in critical care. Along with anatomical challenges, there are physiological compromises those make patient vulnerable to develop acute complications during intubation. Cancer patients can have anticipated difficult airway because of head neck tumour, acute or impending upper airway obstruction, anatomical distortion following surgery or radiotherapy around the airway. In addition to conventional assessment, objective scoring system like MACOCHA score [18] can be very helpful to assess difficult airway. It takes into consideration underlying pathology (coma, severe hypoxia) and the skill of the operator. With a cut off value of 3, it has a good sensitivity (76%) and negative predictive value (97%). Intubation difficulty scale (IDS) is a combination of objective and subjective scoring system to measure difficulty of intubation both qualitatively and quantitatively [19].

The complication data related to predictive score can be correlated clinically. Studies have shown that airway management related complication rate varies with different clinical setting. While intubation failure is a rarity in planned surgical procedures (1 in 2000); in emergency and ICU set up, it can be as high as 1 in 50 procedures [20]. Among standard anatomical airway assessments, few findings are common in head neck cancer patients like restricted mouth opening, restricted neck mobility, stiffened submental soft tissue, decreased space within oral cavity and overall distorted normal anatomy, especially after surgery or radiotherapy. Physiological challenges that make intubation difficult in this sub-group are hypoxaemia, hypotension and right heart dysfunction [21].

Ventilation: Among the cancer patients who require ICU admission, almost 50–70% need mechanical ventilation. About half of them need ventilatory support on admission and rest require ventilatory support during their ICU stay because of clinical deterioration. Incidence of invasive ventilation is higher in surgical patients compared to medical one, mostly because of less use of NIV in surgical patients; but the overall mortality is comparable (approximately 20%). Ventilatory management of respiratory failure including ARDS in cancer patients are same like any other non-cancer patients. More than 95% mechanically ventilated patients are managed with conventional mode on ventilator. Non-conventional modes like biphasic positive airway pressure (BiPAP) ventilation, airway pressure release ventilation (APRV), pressure regulated volume control (PRVC), neurally adjusted ventilatory assist (NAVA), proportional assist ventilation (PAV), high frequency oscillatory ventilation (HFOV) are used in a small proportion of cases, especially as rescue therapy in patients with ARDS [22]. Experience of using these non-conventional ventilatory modes in cancer patients is very limited.

Currently ‘Low tidal volume ventilation’ is the standard of care for all ICU ventilated patients with tidal volume 6 ml/kg (range 4–8 ml/kg) of ideal body weight. The original ARMA trial comparing tidal volume 6 vs. 12 ml/kg did not include bone marrow transplant patients or cancer patients with high 6-month mortality [23]. Seong et al. had shown that low tidal volume ventilation is associated with lower mortality (OR 0.37) in ARDS in haematological malignancy [24]. Though volume control mode or pressure control mode did not show any difference in outcome, most of the critical care unit is using volume control mode for its ease of use. Respiratory rate is to be adjusted to achieve targeted minute ventilation. In non

paralysed patient, the set rate should be less than patient's triggered rate by 3–5, so that patient can continue to trigger and there is minimum chance of hyperventilation. FiO_2 should be titrated to achieve SpO_2 92–94%; even lower SpO_2 target of 88–90% is acceptable for patients with chronic obstructive pulmonary disease or ARDS. Setting up of optimal PEEP is challenging in ARDS patients. Routinely, PPEP usually set at 6–8 cm H_2O pressure. In ARDS, optimal titration of PEEP is needed to maintain 'Open lung ventilation' (OLV) strategy—i.e. open the collapsed alveoli with recruitment and keep them open by optimal PEEP. At one hand, suboptimal PEEP will fail to open up basal collapsed alveoli leading to hypoxaemia and atelectotrauma; on the other hand, disproportionately high PEEP will lead to hyperinflation of lung, barotrauma, hypoventilation, right ventricular dysfunction and haemodynamic instability. So, optimisation of PEEP is of paramount importance. There are different techniques that can be used for the same such as (1) by PEEP—FiO_2 contingency table, (2) pressure volume loop, (3) low inflation points, (4) point of maximum curvature or (5) trans-pulmonary pressure etc.

PRCC (Pressure regulated volume control) mode is a hybrid mode currently available in multiple brands of ventilator with different name (e.g. Autoflow in Dragger). It is a pressure regulated and has a decelerating flow pattern; patient ventilator dyssynchrony is apparently less as patient can decide his/ her own flow requirement. Besides, it ensures delivery of targeted tidal volume. It has been compared with volume control or synchronised intermittent mandatory ventilation (SIMV) mode in small trials in patients with ARDS, COPD and traumatic brain injury (TBI). PRVC has consistently shown to decrease peak inspiratory pressure with some improvement in oxygenation [25].

BiPAP & APRV are spectrum of biphasic ventilation. These are closed loop, partial support, time cycled, pressure-controlled mode with two pressure settings at two different level (P high & P low). The difference is in inspiratory to expiratory (I: E) ratio—T high & T low. BiPAP has normal I:E ratio, but APRV has reverse I:E ratio leading to generation of an auto-PEEP leading to some recruitment. These modes have some benefits. In experimental animal model, these have shown to reduce markers of inflammation, apoptosis, fibrinogenesis and epithelial/ endothelial damage compared to conventional modes. APRV reduces endothelial permeability and preserved surfactant proteins A and B concentrations. Other potential benefits are decreased intra-thoracic pressure, improved venous return, increased cardiac output and higher oxygen delivery. Biphasic modes have been compared with conventional modes and also with HFOV (specially in children) without any significant improvement in outcome [26].

Among high frequency ventilations (HFV), high frequency oscillatory ventilation (HFOV) was most widely used, which uses the respiratory frequency is >2 Hertz and provides low tidal volume less than the dead space. The proposed mechanisms for gas exchange are convective ventilation, Taylor dispersion, the Pendelluft effect, cardiogenic mixing, molecular diffusion and asymmetrical velocity profiles. Because of two large randomised control trials—OSCAR and OSCILLATE trial, use of HFOV has significantly decreased in ICU.

Like other ARDS patients, recommendation for prone ventilation is same for oncology patients; i.e., moderate to severe ARDS with PaO_2/FiO_2 ratio <150.

PROSEVA trial has shown 28- and 90-day mortality benefit with prolonged proning (>16 h a day) in severe ARDS patients [27].

d. ECMO: Cancer is not an absolute contraindication of extra corporeal life support. In patients with 'full code' management i.e., for patients with cancer in remission or under curative intent of therapy, ECMO can be considered for reversible cardiorespiratory failure like pneumonia, ARDS, pulmonary embolism, diffuse alveolar haemorrhage etc. Literatures for ECMO in cancer patients are very limited. ESLO registry [28] over 17 years period (1992–2008) had shown only 72 cases with 65% solid tumour and rest haematological malignancy and bone marrow transplant, with equal proportion of veno-venous and vino-arterial ECMO. Mortality is very high with haematological malignancy. In another multi-center trial (IDEA study) [29], out of 225 immuno-compromised patients 30% suffered from haematological malignancy and 19% are having solid tumour. Malignancy is associated with worse outcome compare to any immune-suppressed state. Elderly, prolonged mechanical ventilation, hypercapnia, and higher driving pressure prior to ECMO are associated with poor prognosis. Six-month mortality is around 80%. So appropriate selection of cases is of paramount importance.

11.2 Conclusion

Outcome of cancer patients is improving over time. With better chemotherapeutic agents and recent usage of immunotherapy, lots of cancer patients are coming to ICU with "full code". Acute deterioration because of reversible factors like infection should be treated with aggressive medical management including organ supports. Invasive ventilation should be offered, when indicated, as per clinical status of the patient.

Key Points

- Respiratory failure is the most common cause of ICU admission and major cause of death in cancer patients
- It can be related to malignancy per se and related therapy or absolutely unrelated to it.
- Besides underlying respiratory pathology, respiratory support may be needed depending on status of underlying malignancy, its treatment plan and anticipated outcome.
- Noninvasive ventilation or HFNC can be a good therapeutic option specially for haematological malignancy or post bone marrow transplant patients
- When indicated, invasive ventilation should not be delayed or denied as it can cause poor outcome
- Invasive ventilatory strategy in cancer patients is same like non cancer patients and no conventional or unconventional mode has shown any superiority over others.
- Role of extra corporeal support like ECMO in cancer patients need further research.

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