Intensive Care of the Cancer Patient: Current and Future Directions

December 9, 2017
Stephen M. Pastores, MD, MACP, FCCP, FCCM
Program Director, Critical Care Medicine
Vice-Chair of Education
Department of Anesthesiology and Critical Care Medicine
Professor of Medicine in Anesthesiology and Medicine
Weill Cornell Medical College

Disclosures

• Grant Support (MSKCC PI)
  • Asahi Kasei (SCARLET Sepsis Trial)
  • Spectral Medical (EUPHRATES Sepsis Trial)
  • Bayer HealthCare (inhaled amikacin for Gram-negative pneumonia)
• Advisory Board: Theravance, Bayer

Outline

• Survival trends in cancer pts admitted to ICU
• Prognostic factors for mortality
• Respiratory failure: diagnosis & management
• Role of “ICU Trial” and triage criteria
• Future Directions

Cancer statistics, 2016 (USA)

• 1,685,210 new cancer cases
• 595,690 deaths from cancer

American Cancer Society
Global Cancer Statistics

- 14.1 Million new cancer cases
- 8.2 Million deaths from cancer

Critical Care of Cancer Patients

- 5-10% of cancer patients will develop a life-threatening condition requiring ICU admission

- Cancer pts account for 14-22% of all ICU admissions

Major Changes in Care of Critically Ill Cancer Patients

- # of cancer pts needing ICU care has dramatically increased
- ICU survival is now the rule and >50%
- Many classic mortality predictors no longer relevant
- Noninvasive Dx & Rx have allowed new clinical approaches for high-risk cancer pts
- Given poor reliability of triage criteria for ICU admission, new modalities of ICU admission have been designed

Reasons for ICU Admission of Cancer Patients

- Infections: Pneumonia, Sepsis
- Respiratory failure: Infectious/Noninfectious
- High-risk surgery/Post-surgical complications
- Onc emergencies (tumor lysis syndrome, hypercalcemia)
- Neurologic: seizures, PRES
- Cardiovascular: ACS, CHF, Arrhythmias
- Adverse drug reactions: anaphylaxis, ATRA, cytokine release syndrome, thrombotic microangiopathy (TMA)

**Mortality Trends in Critically Ill Cancer Patients**

- Zuber et al. [6]
- Khassawneh et al. [11]
- Azoulay et al. [12]
- Legrand et al. [7]
- Peigne et al. [10]

**Survival Trends of Cancer Patients Admitted to ICU**

- ICU, Hospital and 1yr survival rates have been increasing

**Outcomes of Critically Ill Patients With Hematologic Malignancies: Prospective Multicenter Data From France and Belgium—A Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique Study**

- N=1,011 patients
- 38% with newly diagnosed malignancies
- 25% s/p HSCT (145 allogeneic)
- 23% in remission
- Reasons for ICU admission:
  - Acute respiratory failure: 63%
  - Shock: 42%

- Hospital survival rate: 61%
- 90-day survival: 53%
- 1-year survival: 43%
- Poor performance status, Charlson comorbidity index, allogeneic HSCT, SOFA score assoc. with higher mortality
Systematic review (48 studies, >25,000 pts)
- Mean hospital mortality: 38%
- Higher mortality with:
  - Poorer physiological status
  - Invasive mechanical ventilation
  - Poor functional status

Mortality Trends in HSCT vs. Non-HSCT Patients in ICU
Azoulay E, Soares M, Darmon M, Beroll D, Pastores S, Alessa B. Ann Intensive Care 2011;1:5
- N=161, MSKCC ICU
- ICU survival: 65%; Hospital: 46%
- 5-yr survival: 20%
- Poor ICU outcome variables:
  - Use of invasive mechanical ventilation
  - Vasopressors
  - Hemodialysis

Hospital mortality of critically ill patients with cancer-related complications
Torres VBL, et al. (2016), PLOS ONE 11(10): e0164537
- Increased hospital mortality
  - Respiratory failure
  - Vasopressors
  - Cardiovascular complications
  - Hemoptysis
  - Hemodialysis
  - Metastasis
  - Hypertension
  - Urinary tract infection
Improved outcomes in different scenarios…

- Acute kidney injury / Need RRT
  Benoît et al, NDT 2005; Soares et al. JCO 2006; Darmon ICM 2007

- Chemotherapy
  Darmon et al. CCM 2005; Benoît et al, ICM 2006; Vandjiek et al. ICM 2008

- Prolonged ICU
  Soares et al. Chest 2008

- Sepsis/Severe Sepsis/Septic Shock
  Larché et al. ICM 2003; Danai et al. Chest 2006; Père et al. CCM 2008

Classic predictors of mortality are no longer relevant

- Type of malignancy (solid vs. heme)
- Short-term neutropenia
- Recent chemotherapy
- Autologous BMT

Doing everything possible, even cancer chemotherapy, may improve outcome.

Anticancer treatments in ICU

20-yr old man with a high-grade NHL and obstructive ARF

ICU admission
After chemotherapy
Retrospective study, n=37 pts, Jan 1997-March 2005
Mean age 46 yrs; mean APACHE II 23
Reasons for chemotherapy:
– Extensive disease with organ involvement (54%)
– Extensive disease without organ involvement (19%)
– Severe DIC (11%); Others (16%)
62% required mechanical ventilation; 24% RRT
ICU mortality: 48% in ventilated pts vs. 7% non-ventilated
Hospital mortality: 61% vs. 14%
6-mo mortality: 74% vs 54%


Retrospective, n=56, Oct 2006-Nov 2013
88% had hematologic cancer
Median age: 47 yrs; Charlson Comorbidity Index: 3 (2 to 5); SAPS II: 50 (39 to 61)]
MV & vasopressors used in 34 pts (61%), CRRT in 22 (39%), and ECMO in 7 (13%)
ICU mortality: 25%, Hospital mortality: 41%
Hospital survivors:
– Significantly younger
– Lower CCI, SAPS II, & tumor lysis syndrome risk scores
– Presented less often with septic shock
– Less likely to develop TLS
– Received less VP, CRRT, and platelet transfusions
After discharge, 88% continued chemoRx & 69% 1-yr of survivors were in complete remission


Retrospective, n=181, Jan 2010-Dec 2015
Median age: 62 yrs; MPM-II score on ICU admission: 39%
Initiation chemo in 40%, continuation in 60%
MV used in 41%, VP 33%, CRRT 9%
Median ICU LOS: 6 days, Hospital LOS: 22 days
ICU survival: 75%; Hospital: 58%
6-mo survival: 58%; 12-mo 50%
Initiation group:
– More likely to be newly diagnosed
– Lower mortality rate

Outcomes of Hematologic Cancer Patients Receiving Chemotherapy at MSKCC ICU

Outcomes of Hematologic Cancer Patients who received intravenous chemotherapy in the intensive care unit

• 38 studies (N= 6054 pts, 2097 neutropenic), 2005-2015
• Median mortality: 54%
• No significant diff in mortality when adjusted for severity
• ICU admission denial based upon neutropenia should be discouraged

Limitations of Outcome Studies in ICU Cancer Patients
• Most are retrospective & single-centered
• Significant heterogeneity in patient case mix:
  - Medical vs. surgical
  - Solid vs. hematological
  - Allogeneic vs. autologous SCT
• Variations in ICU admission & discharge criteria and settings & timing for EOL decisions

Advances in ICU supportive care

Recent Advances in Intensive Care of Cancer Patients
• Less restrictive admission policies
• Use of noninvasive ventilation
• Diagnostic strategy in acute respiratory failure
• Prevention of tumor lysis syndrome
• Management of acute kidney injury
• Advances in antifungal agents
• Transfusion policies
• Recognizing drug-related organ toxicities

Acute Respiratory Failure in Cancer Patients

• ~ 5% - 10% of all cancer pts will experience ARF.
• Incidence higher in heme malignancies – Up to 50%.
• Solid tumors – higher in lung and H&N
• ARF occurs in up to 88% of non-surgical ICU admissions.
• 44% - 69% require ventilatory support.

Study Hospital mortality
Before 2000
Snow et al. (1979) 180 (87%)
Hauser et al (1982) 24 (75%)
Schuster & Marion (1983) 52 (52%)
Lloyd-Thomas et al (1984) 50 (90%)
Peters et al (1991) 116 (82%)
Egner et al. (1996) 157 (63%)
Groeger et al. (1998) 782 (78%)
Kreis et al. (1999) 153 (67%)
After 2000
Azoulay et al. (2001) 237 (73%)
Khassaech et al. (2002) 70 (74%)
Vallet et al. (2003) 165 (63%)
Azoulay et al. (2004) 148 (82%)
Depuydt et al. (2002) 166 (71%)
Soares et al. (2005) 403 (94%)
Azoulay et al. (2006) 110 (85%)
Lecuyer et al. (2008) 1232 (55%)
Adda et al. (2008) 99 (62%)
Depuydt et al. (2010) 91 (78%)

Mechanically Ventilated Patients

n = 1514 patients
Mortality = 81%

n = 2792 patients
Mortality = 63%

Causes of ARF in cancer patients

Infections
• Bacterial infections
  - Common pyogenic bacteria
  - Intracellular bacteria
  - Other bacteria (Nocardia sp)
• Pneumocystis jirovecii
• Invasive fungal Infections
• Lung involvement during candidemia
• Endemic fungal infections
• Viral infections
• Mycobacterial infections

Noninfectious causes
• Cardiogenic pulmonary edema
• Capillary leak syndrome
• Lung injury
• Radiation-induced toxicity
• Alveolar hemorrhage
• TRALI
• Radiation-induced lung damage
• Alveolar proteinosis
• Diffuse alveolar damage
• Bronchiolitis, BOOP
• Second malignancy

ASH 2016

Toxicities:
• Fever
• Resp failure (capillary leak)
• Vasodilatory shock
• Neurologic

Management:
• Supportive
• Tocilizumab (IL-6 inhibitor)
• Steroids
• 51% overall diagnostic yield for BAL vs. 41% for noninvasive Dx
• 69% yield for infectious etiology.
What this study adds:

- Early FO-BAL is safe BUT adds less diagnostic information than commonly perceived (<20%).
- FO-BAL has little therapeutic impact.
- Noninvasive tests identifies the causes of ARF in most cases and more quickly than FO-BAL.

Azoulay E, AJRCCM 2010;182:1038-46
### Table 2: Outcomes of Treatment

<table>
<thead>
<tr>
<th>Reference</th>
<th>NIV (No. of Patients)</th>
<th>Hospital Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kress et al. [23]</td>
<td>MV 153</td>
<td>67%</td>
</tr>
<tr>
<td>Azoulay et al. [104]</td>
<td>MV 40, NIV 9</td>
<td>79%</td>
</tr>
<tr>
<td>Hilbert et al. [29]</td>
<td>NIV 64</td>
<td>85%</td>
</tr>
<tr>
<td>Standinger et al. [110]</td>
<td>MV 186</td>
<td>77%</td>
</tr>
<tr>
<td>Hilbert et al. [22]</td>
<td>MV 14, NIV 8</td>
<td>MV 93%, NIV 50%</td>
</tr>
<tr>
<td>Azoulay et al. [21]</td>
<td>MV 189, NIV 48</td>
<td>70.8%</td>
</tr>
<tr>
<td>Kassavetis et al. [116]</td>
<td>MV 78</td>
<td>75%</td>
</tr>
<tr>
<td>Darmoon et al. [114]</td>
<td>MV 49, NIV 42</td>
<td>74.5%</td>
</tr>
<tr>
<td>Mounas et al. [113]</td>
<td>MV 48</td>
<td>74%</td>
</tr>
<tr>
<td>Vello et al. [139]</td>
<td>MV 66, NIV 12</td>
<td>79.4%</td>
</tr>
<tr>
<td>Azoulay et al. [4]</td>
<td>MV 114, NIV 79</td>
<td>75%</td>
</tr>
<tr>
<td>Depuydt et al. [140]</td>
<td>MV 444, NIV 19</td>
<td>64%</td>
</tr>
<tr>
<td>Soares et al. [141]</td>
<td>MV 1804, NIV 348</td>
<td>MV 75%, NIV 50%</td>
</tr>
</tbody>
</table>

**NIV ~15%-16% of the patients**

Azoulay and Schlemmer. ICM 2006

---

### Management of Acute Respiratory Failure in Patients With Hematological Malignancy

**Reference**

Kress et al. [23]
Azoulay et al. [104]
Hilbert et al. [29]
Standinger et al. [110]
Hilbert et al. [22]
Azoulay et al. [21]
Kassavetis et al. [116]
Darmoon et al. [114]
Mounas et al. [113]
Vello et al. [139]
Azoulay et al. [4]
Depuydt et al. [140]
Soares et al. [141]

**Hospital Mortality**

MV 153
MV 40, NIV 9
NIV 64
MV 186
MV 14, NIV 8
MV 189, NIV 48
MV 78
MV 49, NIV 42
MV 48
MV 66, NIV 12
MV 114, NIV 79
MV 444, NIV 19
MV 1804, NIV 348

MV 67%
79%
85%
77%
MV 93%, NIV 50%
70.8%
75%
74.5%
74%
79.4%
75%
64%
MV 75%, NIV 50%
Initial treatment with NIV did not improve survival compared to oxygen only.

- ARF causes:
  - Infections (43%)
  - Malignant infiltration (17%)
  - Cardiac pulm edema (10%)

- n=380
- HF oxygen used in 2/5 of pts and may have decreased intubation and mortality rates

- Limitations:
  - Limited power due to lower than expected mortality rate with O2 alone
  - 28 hospitals. France and Belgium, n=374
  - Primary outcome: 28-d mortality
High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure

Multicenter, open-label trial in 23 ICUs, France & Belgium (n=310)
- 3 Arms:
  - High-flow O2
  - Standard O2 via face mask
  - NIPPV
- Significant difference in favor of high-flow oxygen in 90-day mortality.

Post hoc analysis, RCT NIV vs O2 (N=353)
- HFNC did not reduce intubation or survival rates vs. standard oxygen.
- Results possibly due to low statistical power or unknown confounders associated with subgroup analysis.

Prediction is very difficult, especially about the future.

Niels Bohr
Danish physicist (1885-1962)
- Prognostic scores (APACHE II-IV, MPM, ICCM) usually underestimate mortality in ICU pts with cancer.
- Should neither be used on an individual basis nor to guide decisions related to patient care.

Triage Criteria for ICU Admission are Unreliable.
Outcome of Cancer Patients Considered for ICU Admission

N=105/206 pts admitted to ICU
- Refused "too-well" for benefit
- Admitted to the ICU
- Refused "too-sick" for benefit
  (26% were alive on day 30 and 17% on day 180)


At least 3-5 days of ICU management is warranted before making a final decision (ICU Trial).

The ICU Trial

- All cancer patients for whom ICU admission was requested

- Bedridden / Poor PS
  - Palliative care only
  - Refusal ICU admission

- Refusal ICU admission
  - Comfort / palliative care

- New diagnosis or disease
  - First-line treatment
  - Potentially reversible acute complication

- Consider ICU trial if patient / family are willing
  - Proceed ICU admission
  - Full code management

Changes in Logistic Organ Dysfunction Score throughout ICU stay

Nonsurvivors

Survivors

Crit Care Med 2007 Vol. 35, No. 3
The ICU Trial

- None of the variables present on ICU admission was significantly different between ICU survivors and nonsurvivors.
- Only after Day 3, nonsurvivors had significantly more organ dysfunction than ICU survivors.

Crit Care Med 2007 Vol. 35, No. 3

Which Cancer Patients are Unlikely to Benefit from ICU Care?

- Bedridden
- No life-span extending treatment options
- Elderly pts with significant comorbidities
- Multiple or severe comorbidities (COPD, heart failure, cirrhosis)
- Invasive pulmonary aspergillosis requiring invasive MV
- Allogeneic HSCT recipients with severe GVHD
- Solid tumors and:
  - Pulmonary carcinomatous lymphangitis with ARF
  - Carcinomatous meningitis with coma
- MSOF related to delayed ICU admission

Mokart D, Pastores SM, Darmon M. Intensive Care Med 2014; 40:1570

Hospital mortality in patients with delayed ICU admission


Factors Associated with Higher Survival and More Efficient Resource Use:

- Availability of clinical pharmacists in ICU
- Implementation of protocols
- Shared care planning between oncologists & intensivists
ICU Triage of Cancer Patients

- Time-limited Trials
  - Do everything and reassess, for potential and otherwise

- Early ICU admission
  - Patients with cancer or hematopoietic stem cell transplantation

- High risk patients
  - Requires more attention: high illness severity, hematopoietic stem cell transplantation and immunosuppressive therapy

- Home vs. Hospital
  - Home is preferred for patients in whom new drug has been approved

Transitioning to End-of-Life Care

- 3.5% to 27% of elderly pts (>65 yrs) with cancer in developed countries had at least one ICU admission during their last 30 days of life (JAMA 2016).
- ICU admissions 2x more in US than in other countries
- Geographic variation in frequency of withholding or withdrawal of life-prolonging treatment
- Physician beliefs & attitudes are major determinants
- Clinicians should try to discuss EOL issues & palliative care with cancer pts early after diagnosis to avoid futile care.


Future Directions

- Early ICU admission
- Alternatives to intubation with ARF
- Diagnostic strategies for infection
- Tailoring therapy to biomarkers
- Impact of critical illness on long-term outcomes
- Understanding/Rx toxicity of targeted Rx & biotherapy
- Transfusion policies
- Moving back from noninvasive to invasive management
- Rescue strategies for cancer patients with ARDS
- Hematopoietic stem cell transplantation in the ICU

Oncological Critical Care Research Network

- Mission:
  - Establish and maintain a global collaborative infrastructure for oncologic critical care research and through research and education reduce the burden of critical illness in cancer patients around the world
- Leadership and Collaborators:
  - MD Anderson Cancer Center
  - Johns Hopkins
  - Memorial Sloan Kettering Cancer Center
  - UC San Diego
  - Barnes-Jewish Hospital
  - Cooper Health
  - Duke University Medical Center

http://www.oncccrnet.org/
Critical Care of Cancer Patients
Summary

- Prognosis of critically ill pts with cancer has improved over the past two decades.

- Classic predictors no longer predictive of ICU survival.

- ICU Trial reasonable in selected pts with close collaboration among oncologists, palliative care, and intensivists.

- More collaborative studies needed to evaluate impact of ICU on overall long-term & disease-free survival.

Thank you
pastores@mskcc.org