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CONFERENCE REPORTS AND EXPERT PANEL

Critically ill cancer patient's resuscitation: a Belgian/French societies' consensus conference

Anne-Pascale Meert[1*], Sebastian Wittnebel[2], Stéphane Holbrechts[3], Anne-Claire Toffart[4], Jean-Jacques Lafitte[5], Michael Piagnerelli[6], France Lemaitre[7], Olivier Peyrony[8], Laurent Calvel[9], Jean Lemaitre[10], Emmanuel Canet[11], Alexandre Demoule[12], Michael Darmon[13], Jean-Paul Sculier[1], Louis Voigt[14], Virginie Lemiale[13], Frédéric Pène[15], David Schnell[16], Etienne Lengline[17], Thierry Berghmans[18,19], Laurence Fiévet[18], Christiane Jungels[18], Xiaoxiao Wang[18], Ionela Bold[18], Aureliano Pistone[18], Adriano Salaroli[2], Bogdan Grigoriu[1] and Dominique Benoit[20] on behalf of the Critically ill cancer patients consensus conference group

Abstract

To respond to the legitimate questions raised by the application of invasive methods of monitoring and life-support techniques in cancer patients admitted in the ICU, the European Lung Cancer Working Party and the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique, set up a consensus conference. The methodology involved a systematic literature review, experts' opinion and a final consensus conference about nine predefined questions

1. Which triage criteria, in terms of complications and considering the underlying neoplastic disease and possible therapeutic limitations, should be used to guide admission of cancer patient to intensive care units?
2. Which ventilatory support [High Flow Oxygenation, Non-invasive Ventilation (NIV), Invasive Mechanical Ventilation (IMV), Extra-Corporeal Membrane Oxygenation (ECMO)] should be used, for which complications and in which environment?
3. Which support should be used for extra-renal purification, in which conditions and environment?
4. Which haemodynamic support should be used, for which complications, and in which environment?
5. Which benefit of cardiopulmonary resuscitation in cancer patients and for which complications?
6. Which intensive monitoring in the context of oncologic treatment (surgery, anti-cancer treatment …)?
7. What specific considerations should be taken into account in the intensive care unit?
8. Based on which criteria, in terms of benefit and complications and taking into account the neoplastic disease, patients hospitalized in an intensive care unit (or equivalent) should receive cellular elements derived from the blood (red blood cells, white blood cells and platelets)?
9. Which training is required for critical care doctors in charge of cancer patients?

Keywords: ICU, Critically ill, Cancer, Haematological

*Correspondence: ap.meert@bordet.be
[1] Service de Médecine Interne, Soins Intensifs et Urgences Oncologiques, Institut Jules Bordet (Université Libre de Bruxelles, ULB), Rue Héger-Bordet, 1, 1000 Brussels, Belgium
Full author information is available at the end of the article

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Introduction

Life-support techniques considerably evolved since the middle of the twentieth century. Numerous developments have made possible to compensate various organ failure by means of invasive and non-invasive mechanical ventilators, cardiac resuscitation haemodialysis and extracorporeal membrane oxygenation (ECMO). At the same time, the outcomes of patients suffering from a malignant oncological or haematological condition have been considerably improved [1] justifying exploration of resuscitation techniques in such patients.

The initial studies published in the years 1970–1990 showed the feasibility of intensive care in oncological patients despite an often poor outcome; however, this prognosis has changed profoundly over the past 20 years.

To respond to the legitimate questions raised by the application of invasive methods of monitoring and life-support techniques, the European Lung Cancer Working Party (ELCWP) and the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (Grrr-OH), two academic cooperative groups, set up a consensus conference in Brussels on December 5–7 2019. The methodology, based on that used by the Belgian national health insurance organization (INAMI), involved a systematic literature review, experts' opinion and a final consensus conference about nine predefined questions. Here we report on the final text of consensus conference.

Methods

Members of the European Lung Cancer Working Party (ELCWP) and the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (Grrr-OH), two academic cooperative groups, acknowledged the need of a consensus conference about the critically ill cancer patient on October 2017. They used a methodology similar to the consensus conference organized by the Belgian national health insurance organization (INAMI) [2].

The organizing committee of this consensus conference consisted of five experts clinicians: Anne-Pascale Meert (intensivist, Bordet Institute, Brussels, Belgium, President), Dominique Benoit (intensivist, Ghent university, Belgium, Vice president), Elisabeth Quoix (chest physician, Strasbourg, France), Nathalie Meuleman (haematologist, Bordet Institute, Belgium), Djamel Mokart (intensivist, Marseille, France) and a methodologist Alain Vanmeerhaeghe (Charleroi, Belgium). According to the methodology applied for consensus conference, nine questions were formulated by the consensus conference organizing committee following a modified Delphi method (including 3 rounds).

Take-home message

We report the results of a consensus conference based on a systematic review of the literature and experts opinions assessing the management of cancer patients in the ICU.

Research questions:

1. Which triage criteria, in terms of complications and considering the underlying neoplastic disease and possible therapeutic limitations, should be used to guide admission of cancer patient to intensive care units?
2. Which ventilatory support [High Flow Oxygenation, Non-invasive Ventilation (NIV), Invasive Mechanical Ventilation (IMV), Extra-Corporeal Membrane Oxygenation (ECMO)] should be used, for which complications and in which environment?
3. Which support should be used for extra-renal purification, in which conditions and environment?
4. Which haemodynamic support should be used, for which complications, and in which environment?
5. Which benefit of cardiopulmonary resuscitation in cancer patients and for which complications?
6. Which intensive monitoring in the context of oncologic treatment (surgery, anti-cancer treatment …)?
7. What specific considerations should be taken into account in the intensive care unit?
8. Based on which criteria, in terms of benefit and complications and taking into account the neoplastic disease, patients hospitalized in an intensive care unit (or equivalent) should receive cellular elements derived from the blood (red blood cells, white blood cells and platelets)?
9. Which training is required for critical care doctors in charge of cancer patients?

Subsequently, the organizing committee identified and invited the members of the systematic review panel, the expert panel and the jury.

The expert panel was composed of French and Belgian members of the ELCWP and Grrr-OH who are used to manage critically ill cancer patients and perform research in this field for more than 20 years.

The organizing committee proposed the jury which may reflect all the people involved in the real life in decision making process of cancer patients in the intensive care unit (ICU): general ICU specialists not experts in cancer resuscitation, emergency doctor, oncologist, hematologist, surgeon, pulmonologist, palliative care specialist, a patient representative and a nurse.

None of them declared conflicts of interests with regard to the research questions.

The committee organized the consensus conference on December 5–7 2019. The results of the systematic review were presented and discussed by experts followed by a questions/answers session with the jury (and the public).

The jury has to provide at the end of the conference a consensual text (conclusions and recommendations) with a precise answer to each of the questions based on the literature review, the presentations by the experts and the questions/ answers session. The text was written on the third day of the conference.

Systematic review

According to the methodology applied for consensus conference, nine questions were formulated by the consensus conference organizing committee following a modified Delphi method. These questions were provided to a bibliographic research group (Thierry Berghmans, Valérie Durieux, Laurence Fiévet, Christiane Jungels, Xiaoxiao Wang, Ionela Bold, Aureliano Pistone, Adriano Salaroli, Bogdan Grigoriu) which was independent of the working group (jury) and experts invited to interpret the selected literature. The aim of this work is to provide a systematic review of objective literature for each question. No interpretation of the data collected will be provided.

The literature search was carried out from January 2018 until January 2019 using the Ovid Medline database. The formulation of the research equations was carried out jointly by a doctor specialized in oncology, and trained in resuscitation and management of oncological emergencies, and by a librarian expert in the conduct and realization of systematic reviews. The PICO (Population/Intervention/Control/Outcome) model was used to identify the concepts included in each question. The corresponding search criteria were translated into MeSH descriptors and into keywords (free language), and were searched in the titles, summaries and names of the substance. These equations were then independently reviewed by a second doctor with the same training in oncology and resuscitation. The selection of eligible articles was carried out according to the methodology described below, in pairs so that the selection of articles and the extraction of data were validated consensually by two doctors.

Selection of articles:

- *First step*: A first selection of articles was done on the basis of the title and content of the summaries. Any article potentially eligible for the specific question was retained for the next step, blinded to the language used in the publication. The choice of abstracts was made blind in each reading group. Any reference selected by at least one of the two readers was considered for the next step. To obtain the most exhaustive review possible, "noise" (articles not eligible for systematic review) was considered acceptable.
- *Second step*: For all the articles selected during the 1st stage, full-length publications were available to the readers in a specific Dropbox. These articles were analysed on the basis of the full publication to determine their eligibility for systematic review.
- *Third step*: the eligible articles were subsequently analysed to extract the required data on the basis of an Excel file adapted to each question (data common to all the questions plus specific data). The content of the file was designed by the two expert doctors and validated/ completed by the other physicians before and during the analysis of the articles.

Prospective studies, retrospective studies (including a minimum of 14 patients; choice of this threshold based on the design proposed by Simon), systematic qualitative review and systematic quantitative review with data aggregation (meta-analysis) were considered for the systematic review. Only studies whose publication was available in one of the languages accessible to the readers were selected: French, English, Dutch, German, Spanish or Italian. To be eligible, the study had to focus only on patients with cancer pathology; in the case of studies involving other types of patients, the results for the cancer patient subgroup had to be available.

The initial list of articles obtained by the search equations was provided to readers without mention of the language of publication. To assess the potential bias linked to the selection on the basis of languages accessible to readers, the librarian then distributed the references selected in the 1st step according to the language of publication.

This systematic review is available as online appendix.

Experts opinion

In a second step, recognized experts (Emmanuel Canet, Alexandre Demoule, Michael Darmon, Jean-Paul Sculier, Louis Voigt, Virginie Lemiale, Frédéric Pène, David Schnell, Etienne Lengline) in the relevant field (reflecting the range and diversity of known opinions on the subject) received the systematic review text.

Their roles were to comment on the results of research in the literature, to give their interpretation of the literature, justifying their statements by referencing them and to write a text sent to the members of the jury and to provide a precise answer to the questions of the jury during the conference consensus.

The experts' opinion is available as online appendix.

Consensus conference

The third step consisted in the consensus conference that was held on December 5–7 2019.

The jury was composed of general intensivists (Michael Piagnerelli, France Lemaitre), emergency doctor (Olivier Peyrony), oncologists (Stéphane Holbrechts, Anne-Claire Toffart), pulmonologist (Jean-Jacques Lafitte), haematologist (Sebastian Wittnebel), palliative care specialist (Laurent Calvel) and a thoracic surgeon (Jean Lemaitre) as well as a patients' representative of the VAINCRE association (Dominique Peltgen) and a nurse (Nathalie Leclercq). Members of the jury cannot have financial or any other conflict of interests that could influence the process. They are not experts and must not have taken a recent well-known and committed public position on the subject dealt with the conference. The consensus conference was held in French and was open to everyone including patients. Consensus conference was open to everyone including patients.

On December 5–6 2019, the results of the systematic review were presented and discussed by experts followed by a questions/answers session with the jury (and the public). The systematic review was available to the experts before the conference.

The jury has to provide at the end of the conference a consensual text (conclusions and recommendations) with a precise answer to each of the questions on the basis of the literature research, the experts 'presentations and the questions/answers session. The text was written the third day of the conference. Only selected citations which helped in formulating the recommendations are given in the consensus text. We refer to the systematic review (suppl 1) for a comprehensive review of the literature.

Level of proof

GRADE A. High level of evidence

It means that a conclusion is based on Randomized Controlled Trials (RCTs—Randomized Clinical Studies) of excellent methodological quality and that the results are consistent for several studies.

GRADE B-Moderate level of evidence

It means that a conclusion is based on RCTs with serious methodological limitations (serious limitations) or that several studies show inconsistent results.

GRADE C. Low (or very low) level of evidence

It means that a conclusion is based on RCTs with very serious methodological limitations (very serious limitations) or that a conclusion is based on RCTs with serious methodological limitations (serious limitations) and that several studies show inconsistent results.

Recommendation levels

Strong recommendation

The advantages of a specific intervention or action clearly outweigh the disadvantages or risks.

Low recommendation

There is a balance between the advantages and the disadvantages or risks of a particular intervention or action.

The consensus conference report will be updated if new data are available.

Consensus conference report

Q1- Which triage criteria, in terms of complications and considering the underlying neoplastic disease and possible therapeutic limitations, should be used to guide admission of cancer patient to intensive care units?

The main objective of this analysis is to identify reasons for ICU admission and/or refusal in cancer patients with an acute life-threatening complication (excluding programmed surgery and preventive monitoring).

Q1.1 Indications of ICU admission

Sepsis and respiratory failure are the main reasons for ICU admission in cancer patients [3].

Several observational studies have reported that early ICU referral was associated with decreased in-hospital mortality [4–7]. Several scores measuring variations in key physiological and biological parameters (qSOFA, SOFA, NEWS…) may help doctors in identifying patients at risk of organ failure early in the course of their disease. However, their applicability and their ability in predicting patients' individual prognosis are insufficient to recommend their use during triage decisions [8, 9].

Recommendations

- In hospital wards, patients with cancer should be screened for acute organ dysfunction. (*Grade B, strong recommendation*)
- ICU admission should be discussed as soon as acute organ dysfunction occurs. (*Grade B, strong recommendation*)
- ICU admission for critically ill cancer patients should not be delayed. (*Grade B, strong recommendation*)

Q1.2 Triage criteria for ICU admission

First of all, it is important to acknowledge, timely the patient's wishes and goals concerning life-sustaining therapy in the ICU in case of severe deterioration. Hereby it is important to taken the general condition of the patient into account.

Second, the prognosis related to the acute complications and to the underlying cancer should be taken into account. Most cancer related-characteristics (type of cancer, histopathology, etc.) have little impact on the likelihood of survival in the ICU [10–12]. Conversely, baseline health status (evaluated by the performance status), the burden of chronic comorbidities, and the number and severity of organ dysfunctions at ICU admission are identified as the main predictors of ICU survival [3, 13–16].

Recommendations

- Full code ICU management should be offered to cancer patients with good general condition with prolonged life expectancy (ECOG Performance Status 0–2), particularly with a cancer in remission or with an ongoing cancer treatment. (*Grade C, strong recommendation*)
- Cancer patients with a poor general condition (ECOG Performance Status 3–4) within 1 month prior to ICU admission, patients who are not or no longer eligible for cancer treatment, or patients with a very short life expectancy should probably not benefit from an ICU admission. (*Grade C, strong recommendation*)
- Patients with controlled cancer and a good general condition should probably be admitted to ICU. The therapeutic strategies should be determined, the intensity of care should be defined according to the reversibility of the acute complication, and the efficacy of initiated treatments should be regularly evaluated. (*Grade C, strong recommendation*)

Q1.3 Evaluation of the ICU management over time

The concept of ICU trial appeared in the early 2000s. The idea was to provide full ICU support to some patients with an uncertain prognosis, but for a limited duration. Initially it was proposed to reappraised the situation of the patient after 3–5 days of full ICU support via daily interdisciplinary meetings between intensivist and oncologist / haematologist. However, whereas according to a recent study a 2–4 days ICU trial seems sufficient to discriminate survivors from non-survivors in cancer patients with an unfavorable prognosis, an ICU trial of 10–14 days would be necessary in other situations. There is insufficient data in the literature to make a recommendation concerning the time frame [17].

Recommendations

- The efficacy and intensity of ICU care should be evaluated daily by both intensivists and oncologists/haematologists. (*Grade C, strong recommendation*)

Q1.4 Hematopoietic stem cell transplantation and ICU support

The prognosis of allogeneic hematopoietic stem cell transplant patients admitted to the ICU has improved over time [18, 19]. However, this improvement is mainly observed in patients without invasive ventilation, without acute graft-versus-host disease, and with a limited number of organ failures (≤ 2).

Recommendations

- ICU management should probably be offered to allogeneic hematopoietic stem cell transplant patients as soon as acute organ dysfunction occurs. Patient and the evolution and the severity of organ failure should be reassessed on a regular basis. (*Grade C, strong recommendation*)
- Invasive mechanical ventilation should probably not be implemented or prolonged in allogeneic HSC recipients who develop uncontrolled acute graft versus host disease and multiple organ failures. (*Grade C, strong recommendation*)

Q2. Which ventilatory support [High Flow Oxygenation, Non-invasive Ventilation (NIV), Invasive Mechanical Ventilation (IMV), Extra-Corporeal Membrane Oxygenation (ECMO)] should be used, for which complications and in which environment?

Q2.1 Standard oxygen therapy

We identified four randomized controlled trials (RCTs) and one meta-analysis [20–24]. These studies did not show any benefit of standard oxygen therapy in comparison to room air to relieve dyspnea in patients with advanced cancer. However, these studies do not allow us to respond to the question concerning the benefit of standard oxygen delivery for cancer patients admitted in the ICU with acute respiratory failure.

Recommendations

- Standard oxygen therapy should probably not be administered in a palliative setting with the only intention to reduce dyspnea. (*Grade B, strong recommendation*)
- Standard oxygen therapy should be administered to cancer patients admitted in the ICU with acute respiratory failure to achieve $SpO_2 > 90\%$. (*Expert opinion, strong recommendation*)

Q2.2 High-flow nasal oxygen (HFNO)

Seven studies compared HFNO to standard oxygen therapy. Two of these studies were RCTs and included

immunocompromised patients with a large proportion of malignancies [25, 26]. These studies did not show any reduction in mortality or intubation rate. The results of retrospective studies are discordant. Three did not show any benefit in mortality or intubation rate [27–29]. One showed a decrease in 28-day mortality but in this study patients received HFNO and non-invasive ventilation (NIV) [30]. The last study showed a reduction in intubation rate, without, however, a reduction in hospital mortality [31].

Recommendations

- HFNO should probably not be administered systematically instead of standard oxygen therapy in cancer patients admitted in the ICU with acute respiratory failure. (*Grade A, strong recommendation*)
- If HFNO is used, it should be limited to patients without altered level of consciousness and without organ dysfunction other than respiratory failure. HFNO should be provided for a limited duration. Close monitoring in the ICU enables early reevaluation of its efficacy. (*Expert opinion, strong recommendation*)

Q2.3 Non invasive ventilation (NIV)

The data relative to the benefits of NIV are conflicting. Twenty years ago, Hilbert et al. compared NIV to standard O_2 therapy in an RCT that included 54 immunocompromised patients with fever, pulmonary infiltrates and acute respiratory failure. Patients receiving NIV had a lower intubation rate and mortality [32]. These results could not be confirmed in a more recent large RCT [33]. This may be explained by a significant improvement in supportive care of critically ill oncologic patients over the past decades with a subsequent reduction in mortality as a consequence. Nevertheless, it is important to note that NIV failure in observational studies is associated with a higher mortality than early intubation [34–37].

Recommendations

- Although there is no specific data available on cancer patients, NIV should be administered to cancer patients with cardiac pulmonary oedema or chronic obstructive pulmonary disease exacerbation (with respiratory acidosis). (*Grade B, strong recommendation*)
- NIV should probably not be initiated in cancer patients admitted in the ICU with acute respiratory failure (except exacerbation of chronic obstructive pulmonary disease or cardiac pulmonary oedema). This is more specifically true in patients with severe respiratory failure (polypnea, acute respiratory distress syndrome (ARDS), severe hypoxia), septic shock, respiratory failure combined with other organ failures (altered level of consciousness, need for vasopressors, renal replacement therapy) and delayed ICU admission. (*Grade B, strong recommendation*)
- However, if NIV is started, patient should be admitted to the ICU to allow close monitoring and frequent reassessments of its efficacy. Intubation should not be delayed in the absence of rapid improvement. (*Expert opinion, strong recommendation*)

Q2.4 Invasive mechanical ventilation (IMV)

Given that IMV appears to be the last therapeutic option in case of severe clinical deterioration, it is difficult to assess its relevance. However, it seems that delayed intubation (after NIV of HFNO failure) is associated with worst outcome [35]. The absence of diagnosis of the acute respiratory failure is also associated with worst outcome [31]. The benefit of an earlier intubation of patients with an unknown diagnosis to perform the most complete diagnostic procedure (including easy access to computed tomography scan and bronchoalveolar lavage) remains to be determined [38].

Recommendations

- Because IMV is initiated in case of failure of other less invasive ventilator techniques, it is impossible to make a recommendation about IMV initiation. (*Expert opinion, strong recommendation*)
- Intubation and IMV should not be delayed in case of absence of rapid clinical improvement with HFNO or NIV or to perform diagnostic procedures if necessary. (*Grade C, strong recommendation*)

Q2.5 Extra-Corporeal Membrane Oxygenation (ECMO)

Six retrospective studies with small sample sizes assessed VV-ECMO in cancer patients [39–44]. These studies showed a high short-term mortality which exceeded the mortality reported in patients without cancer. Patients with haematological malignancies seemed to have worse outcomes [39].

Recommendations

- VV-ECMO should be considered only in cancer patients with an excellent health status (WHO performance status < 2) and a good expected long-term prognosis. Indication should be discussed on a case-by-case basis between intensivists specialized in the treatment of patients with severe ARDS and haemato-oncologists. (*Expert opinion, low recommendation*)

Q3. Which support should be used for extra-renal purification, in which conditions and environment?

Thirty-six studies were eligible for the systematic review [45–80]. The study did not adequately assess the extra renal replacement (RRT) modalities, the timing of its initiation, and the impact of these strategies on patient outcomes.

Nevertheless, two subgroups have been identified:

a. The subgroup of patients with multiple myeloma for which randomized studies evaluate the benefit of extra-renal treatment of light chains in myeloma cylinder nephropathies ("CAST NEPHROPATHY").
   Two extra renal epuration techniques have been evaluated in low-level studies with a small sample size. These studies suggest that plasma exchange and high cutoff membranes should not be used for the sole purpose of treating cast nephropathy [49, 80–83].
b. The subgroup of patients at high risk of tumor lysis syndrome [50, 53, 79, 84–86]. Even if Rasburicase rapidly breaks down serum uric acid, and is effective in preventing and treating hyperuricemia and tumor lysis syndrome, these patients are at high risk of developing acute renal failure and at high risk of death once acute renal failure appears. Moreover, patients with high grade malignancies (acute myelogenous and lymphoblastic leukemia and high grade lymphoma) developing acute renal failure are at increased risk of induction failure.

Recommendations

- It is probably advisable to recommend a RRT strategy in cancer patients similar to the general ICU population. The type RRT modality (acute intermittent vs. continuous or early vs. late) should be tailored to the local expertise. (*Expert opinion, low recommendation*)
- It is probably necessary to admit patients at high risk of tumor lysis syndrome in the ICU. (*expert opinion, low recommendation*)
- Close collaboration between the onco-haematologist and intensivist is essential for the optimal management of tumor-lysis syndrome and the underlying malignancy. (*Expert opinion, strong recommendation*)
- The use of an early RRT strategy is not validated in patient with tumor lysis syndrome but is supported by indirect physiopathological arguments (purification of phosphates considered as a cause in the development of the acute renal failure), by the severity and its consequences. RRT can, therefore, be proposed as a metabolic control technique in patients with tumor lysis syndrome who do not respond to optimal medical treatment. (*Expert opinion, strong recommendation*)
- In the case of intermittent haemodialysis, a risk of rebound of tumor lysis syndrome with metabolic abnormalities has been reported in case series. In the case of intermittent haemodialysis, it is preferable to initiate repeated iterative daily intermittent haemodialysis sessions. (*Expert opinion, strong recommendation*)
- Plasma exchange and high cutoff membranes should not be used for the sole purpose of treating cast nephropathy. (*GRADE B, strong recommendation*)

Q4. Which haemodynamic support should be used, for which complications, and in which environment?

None of the studies selected by the systematic review provides useful information for establishing guidelines specific to oncological intensive care. Given the lack of specific data, it is necessary to apply the recommendations currently proposed in general intensive care in oncological care [87, 88].

Recommendations

- International guidelines for management of shock in critically ill and non-immunocompromised patients admitted to the ICU should be applied to cancer patients. (*Expert advice, strong recommendation*)

Q5. Which benefit of cardiopulmonary resuscitation in cancer patients and for which complications?

A meta-analysis focusing on cancer patients who received cardiopulmonary resuscitation (CPR) showed that the prognosis of these patients was generally worse than that of the general population, and that patients with a metastatic disease had more specifically a grim prognosis [89]. However, the circumstances in which CPR is started and which contribute to mortality (intra or extra-hospital, type of shockable or non-shockable rhythm, control massage, no flow duration) as well as the resuscitation technique are rarely reported. In addition, the management after return to spontaneous rhythm (coronary angiography if necessary, therapeutic hypothermia) is rarely mentioned, whereas Winther-Jensen et al. [90] found that cancer patients received significantly less investigations and treatments compared with the general population. Nevertheless, the authors noticed an improvement in survival over time in this population. Data on physical, emotional and economic complications of CPR in cancer patients and their families are not available.

Recommendations

- Resuscitation decisions in cancer patients must be anticipated and clearly reported in the patient's file grade of recommendation?.
- Except for patients with known therapeutic limitations, cardiopulmonary resuscitation should be performed in cancer patients. (*Expert opinion, strong recommendation*)

Q6. Which intensive monitoring in the context of oncologic treatment (surgery, anti-cancer treatment)?

Monitoring in the ICU may be indicated in two different contexts: post-operative monitoring after oncologic surgery and monitoring during the administration of anti-tumoral treatment with specific side-effects (anaphylaxis…).

Q6.1 Postoperative monitoring

Most studies are retrospective and monocentric with small sample sizes. Nevertheless, these studies found a low likelihood of ICU admission in patients requiring oncological surgery, probably because these patients were already monitored in other facilities.

Recommendations

- It is probably necessary to propose a management protocol for postoperative cancer patients. Such a protocol should take local characteristics (recovery room, post anesthesia care unit) and patients' characteristics (comorbidities and events after surgery) into account. (*Grade C, strong recommendations*)

Q6.2 Monitoring during anticancer treatment

Very little literature exists on the need to monitor patients in the ICU during the administration of anticancer treatment. Studies evaluating the surveillance of patients without organ failure have essentially a retrospective or case–control design, and were performed in specific conditions.

The risk of complications in cancer patients is high and can either be related to the anti-cancer treatments itself (cardiac arrhythmia, anaphylaxis) or to the underlying cancer (tumor lysis syndrome). There are no studies which assessed the benefit of ICU monitoring these subgroups before the onset of organ failure dysfunctions. For new treatments, the risk of developing organ failure is assumed from phase 1 studies. Therefore, recommendations in this experimental field could not be provided. However, the ICU is the most suitable environment to monitor patients at risk of severe complications.

Recommendations

- It is probably necessary to discuss (between intensivist and oncologist) ICU monitoring in the first days of the treatment of an inaugural disease in patients at high risk of immediate serious complications (tumor lysis syndrome, hyperleucocytose, anaphylaxis, arrhythmia, etc). (*Expert opinion, strong recommendation*)

Q7. What specific considerations should be taken into account in the intensive care unit?

Q7.1 Barriers and protection against infection

1) Antibiotic prophylaxis against bacterial infections

Studies of antibiotic prophylaxis in neutropenic patients with solid and haematological malignancies have reported limited and inconsistent benefit on mortality. The use of antibiotic prophylaxis is associated with an increased incidence of bacterial resistance to the molecules used but also of multi-resistant bacteria. No studies have specifically evaluated antibiotic prophylaxis in ICU in cancer patients [91].

Recommendations

- Antibiotic prophylaxis should probably not be given to cancer patients in the ICU, outside the peri-operative setting. (*Expert opinion, low recommendation*)

2) Environmental control

Protective isolation has been shown to be effective in limiting infectious complications and even mortality in neutropenic patients. Protective isolation appears to be most effective in patients with deep (< 500/mm^3) and/or prolonged (> 7 days) neutropenia. However, there is a large variation in protective isolation modalities across studies and not all modalities reduce the risk of airborne contamination with *Aspergillus* spores.

Protective isolation should include geographic isolation (single room), technical isolation (caregivers and visitors dressed with gloves, surgical gown, cap and mask), and surface disinfection. Air filtration (HEPA filter and laminar flow) and an airlock are recommended measures, particularly in the context of deep immunodeficiency. However, these measures must not hinder the quality of care of critically ill cancer patients and should be tailored to the architectural

possibilities of the unit. It should be noted, that in absence of one element of these measures, the benefit of isolation is no longer observed.

It should be noted that this recommendation is based on studies published more than 30 years ago. The reproducibility of these studies in the current practice is uncertain.

Recommendations

- Protective isolation should probably be required for deep ($<500/mm^3$) and/or prolonged (>7 days) neutropenia in critically ill cancer patients. However, the benefit of protective isolation should be outweighed against the risk of adverse events, more specifically in an emergency setting. (*Grade C, strong recommendation*)

Q7.2. Choice of vascular approach and prevention of infections

1) Choice of vascular approach

There is no literature specifically focussing on cancer patients. Therefore, the guidelines for critically ill patients should be applied [92, 93]. However, due to a higher risk of complications (haemorrhagic and infective), a strategy favouring the primary use of a peripheral venous line should be evaluated in the critically ill cancer patients.

Recommendations

- The use of multi-lumen central lines is preferred in ICU. (*Grade C, strong recommendation*)

2) Vascular approach management

Any vascular approach increases the likelihood of infection and thrombosis. Several approaches have been studied: central venous catheter (CVC) (jugular, subclavian or femoral), peripherally inserted central catheter (PICC) or implanted port catheter; however, no studies compared these three modalities together.
Initial peripherally inserted venous line followed by a CVC had more complications compared with the first-line CVC. The average catheter life is 10 days (endpoint: infection). Implanted port catheters have the lowest infection rate, while CVCs have the highest and PICCs have intermediate risk [94].

3) Catheter management

Two methods are described: catheter dressings and the use of antiseptic sponges; their strict application is feasible and is associated with a reduction in catheter-related infections. The use of impregnated catheters is not associated with a reduction of infectious complications or mortality [95].
All data were retrieved from studies performed in the general ICU population which, however, included critically ill cancer patients.

In the absence of specific date, the guidelines for critically ill patients should be applied [93].

Recommendations

- The general guidelines regarding central venous line placement and management are likely to be applicable in critically ill cancer patients. (*Grade C, strong recommendation*)

Q7.3. Integration of Supportive Care in ICU

Nine randomized controlled trials have shown the importance of early supportive and palliative care in the management of cancer patients [96–104]. They focused on the overall management of patients, outside the specific context of ICU.

The use of supportive care is often insufficient and initiated late in the cancer history [105].

Recommendations

- All critically ill cancer patients should receive optimal supportive care before, during and after their ICU stay, in line with their wishes in terms of care intensity, recovery capacities and quality of life in the short and intermediate term [106]. (*Grade C, strong recommendation*)
- Supportive care should probably be started early in cancer patients. (*Grade C, strong recommendation*)

The choice of an integrative, consultative or mixed model is based on local possibilities and the existence of prior multi-disciplinary follow-up (oncologist or haematologist, intensivist, palliative care specialist). Initial and continuing training programs in supportive/palliative care for intensive, oncology and haematology teams should be encouraged.

Q7.4 Which stakeholders should be involved in the management of critically ill cancer patients?

Recommendations

- Consideration should be given to close, multidisciplinary, advanced collaboration along the cancer history including at least the oncologist/haematologist and the intensivist, if necessary expanded to other specialties, to improve the fluidity, efficiency and quality of management of critically ill cancer patients [13]. (*Grade C, strong recommendation*)

Q8. Based on which criteria, in terms of benefit and complications and taking into account the neoplastic disease, patients hospitalized in an intensive care unit (or equivalent) should receive cellular elements derived from the blood (red blood cells, white blood cells and platelets)?

Q8.1 White blood cells transfusion

The prophylactic use of granulocyte transfusion has been abandoned due to the lack of benefits and the advances in conventional therapeutics. Randomized studies and meta-analyses have evaluated the benefit of the therapeutic administration of granulocytes for uncontrolled infections and have not shown a reduction in mortality. High doses of granulocytes have been reported to generate an advantage in overall survival in one study [107] but this finding could not be confirmed in a more recent study [108], suggesting that the improvement in the quality of conventional care has swept away the advantage of this procedure. According to experts, this treatment may still be considered in very selected patients with a localized infection that is poorly under control with a standardized approach.

Recommendations

- Granulocyte transfusions should probably not be offered as systematic adjuvant therapy in critically ill intensive care neutropenic cancer patients with severe infection. (*Grade B, strong recommendation*)

Q8.2 Platelet transfusion

There is no literature specific to intensive care patients and the majority of studies focus on haematological patients. Platelet transfusion strategies can be prophylactic or therapeutic (i.e., for proven hemorrhagic complications). Results of randomized studies and systematic reviews conclude that there is no advantage of the prophylactic approach in terms of mortality; however, prophylactic platelets transfusion decreases the incidence of severe bleeding (Grade III /IV) and increases the duration until the first bleeding. Regarding the transfusion threshold, it appears on the basis of randomized studies and systematic reviews having compared 10×10^9/L to a higher threshold (20–50 10^9/L), that the restrictive approach does not affect survival. However, a lower threshold is safe and decreases the number of platelet transfusions.

Recommendations

- In the absence of data specific to cancer patients in ICU, it is necessary to follow the recommendations of scientific societies.
- A prophylactic transfusion strategy based on a platelet transfusion threshold of 10×10^9 to 20×10^9/L should probably be proposed to cancer patients with hypoproliferative thrombocytopenia in the ICU. (*Grade B, C strong recommendation*)
- In cases of severe bleeding (WHO grades 3 and 4), platelets count should probably be maintained at a level > 50×10^9/L. (*Expert opinion, strong recommendation*)

Q8.3 Red blood cell transfusion

The literature concerning red blood cell transfusions in the ICU is fairly robust (randomized studies, meta-analyses, recommendations) but does not specifically address the cancer population (subgroups). The main issue addressed is the haemoglobin threshold to start transfusion.

In the literature, a so-called restrictive threshold (usually 7 g/dL) is compared with a more liberal threshold (9–10 g/dL). The majority of studies do not find any deleterious effect of the "restrictive" threshold. Three studies have more specifically targeted the oncological population, but the results are discrepant.

Recommendations

- Because the literature did not exclusively target the cancer population admitted in the ICU, the recommendations of scientific societies concerning the general ICU population must be followed.
- It is probably necessary to follow a restrictive erythrocyte transfusion strategy to maintain a haemoglobin level > 7 g/dL in cancer patients with euvolemic anemia admitted in the ICU. This includes patients treated for septic shock. (*Grade B, strong recommendation*)
- The haemoglobin transfusion threshold can be increased between 8 and 10 g/dL in patients with underlying ischemic cardiovascular pathologies. (*Expert opinion, strong recommendation*)

Q9. Which training is required for critical care doctors in charge of cancer patients?

The level of knowledge of onco-haematologists and critical care physicians in their reciprocal discipline has not been addressed in the literature and is, to date, not established or uniformly supported by specific training programs.

A large Brazilian retrospective multicenter study has evaluated the effect of organizational measures in the ICU on the outcome of onco-haematologic patients. The main finding was that daily meetings between the onco-haematologists and the ICU team, and implementation of specific protocols improved the patient's chances of survival.

Training of haemato-oncologist should be focused on early detection of organ failure and timely referral of patients to the ICU. Training of critical care physicians should include diagnosis, prognostication and management of specific complications directly or indirectly related to the underlying cancer.

Recommendations

- Close collaboration between onco-haematologists and the intensive care team, particularly through daily meetings and the implementation of protocols is recommended. (*Grade C, strong recommendation*)
- It is proposed to encourage universities to organize theoretical and practical training as well as continuous formative courses to allow each of the disciplines to acquire sufficient knowledge concerning the managements of cancer patients. (*Expert opinion, strong recommendation*)
- The jury also suggests to setup studies that evaluate the relationship between the quality of communication between teams and outcomes.

Supplementary Information

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Author details

[1] Service de Médecine Interne, Soins Intensifs et Urgences Oncologiques, Institut Jules Bordet (Université Libre de Bruxelles, ULB), Rue Héger-Bordet, 1, 1000 Brussels, Belgium. [2] Service d'hématologie, Institut Jules Bordet (Université Libre de Bruxelles, ULB), Bruxelles, Belgique. [3] Service d'Oncologie, Hôpital Ambroise Paré, Mons, Belgique. [4] Service de Pneumologie, CHU Grenoble, Grenoble, France. [5] Université de Lille, Lille, France. [6] Service de Soins Intensifs, CHU Charleroi Marie, Curie, Université Libre de Bruxelles, 6042 Lodelinsart, Belgique. [7] Service de Soins Intensifs, Namur, Belgique. [8] Service des Urgences, Hôpital Saint Louis, AP-HP, Paris, France. [9] Service de Soins Palliatifs, CHU Strasbourg, FMTS, Strasbourg, France. [10] Service de Chirurgie, Hôpital Ambroise Paré, Mons, Belgique. [11] Service de Médecine Intensive Réanimation, CHU de Nantes, France. [12] Service de Médecine intensive, Réanimation (Département "R3S") and Sorbonne Université, INSERM, UMRS1158 Neurophysiologie respiratoire expérimentale et clinique, AP-HP, Sorbonne Université, Hôpital Pitié-Salpêtrière, Paris, France. [13] Médecine Intensive et Réanimation, Hôpital Saint Louis, AP-HP, Université de Paris, Paris, France. [14] MSKCC, New York, USA. [15] Service de Médecine Intensive, Réanimation, Hôpital Cochin, AP-HP, Centre and Université de Paris, Paris, France. [16] Réanimation et unité de Surveillance Continue, Angoulême, France. [17] Service d'Hématologie Adulte, Hôpital Saint-Louis, AP-HP, Paris, France. [18] Oncology Clinic, Institut Jules Bordet, Université libre de Bruxelles (ULB), Brussels, Belgium. [19] Laboratoire de Médecine Factuelle, Faculty of Medicine, Université libre de Bruxelles (ULB), Brussels, Belgium. [20] Intensive care, Universitaire Ziekenhuis Gent, Gent, Belgium.

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Conflicts of interest

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