REVIEW

Mechanical ventilation in cancer patients

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ABSTRACT

Acute respiratory failure (ARF) in cancer patients remains a frequent and severe complication, despite the general improved outcome over the last decade. The survival of cancer patients requiring ventilatory support in Intensive Care Unit (ICU) has dramatically improved over the last years. The diagnostic approach, including an invasive strategy using fiber optic bronchoscopy or a non-invasive strategy, must be effective to identify a diagnostic, as it is a crucial prognostic factor. The use of non-invasive ventilation (NIV) instead of invasive mechanical ventilation (IMV), has contributed to decrease mortality, but NIV has to be used in appropriate situations. Indeed, NIV failure (*i.e.*, need for IMV) is deleterious. Classical prognostic factors are not relevant anymore. The number of organ failure at admission and over the first 7 ICU days governs outcomes. Ventilatory support can thus be included in different management contexts: full code management with unlimited use of life sustaining therapies, full code management for a limited period, no-intubation decision, or the use of palliative NIV. The objectives of this review article are to summarize the modified ARF diagnostic and therapeutic management, induced by improvements in both intensive care and onco-hematologic management and recent literature data. *(Minerva Anestesiol 2014;80:712-25)*

Key words: Respiration, artificial - Respiratory insufficiency - Prognosis Neoplasms - Hematology - Intensive care units - Mortality.

The number of patients alive with active malignancies is increasing.[1] Outcome in oncology and hematology patients significantly improved over the last decades, since the use of improved diagnostic strategies, the utilization of high-dose chemotherapy, reduced intensity conditioning hematopoietic stem cell transplantation[2] and targeted therapies. These aggressive treatments have decreased cancer mortality, at the price of increased toxic and infectious pulmonary complications, which can require a ventilatory support.

This article aims to review the most recent literature to summarize optimal diagnostic and therapeutic management of acute respiratory failure (ARF) in cancer patients admitted to the Intensive Care Unit (ICU), including clues for the choice of the initial ICU admission criteria and ventilatory strategy, and to highlight the new prognostic factors associated with mortality.

We performed a PubMed search using the keywords "mechanical ventilation", "invasive mechanical ventilation", "non-invasive mechanical ventilation", "acute respiratory failure", "cancer patients", "hematology patients", "oncology", "prognostic factors". All papers that included patients with enough descriptive information were selected for the present review.

Background

ARF is the most frequent, severe and challenging life threatening complication in patients with solid tumors and hematological malignan-

cies.[3] ARF occurs in 5% in patients with solid tumors, 20% in patients with hematological malignancies and up to 40-50% in bone marrow transplantation (BMT) recipients.[4]

For many years, the prognosis of cancer patients admitted to the ICU for ARF was grim, especially when mechanical ventilation (MV) was needed. In the nineties, overall mortality of hematological patients in ICU was 80%, and 90% in BMT recipients.[5] The need for MV, allogenic BMT, and an interval <90 days of BMT prior to ICU admission were independent adverse prognostic factors.[6] Therefore, MV was considered as futile, and ICU admission was seriously debated considering the dismal prognosis.

For the last years, improved survival rates were reported.[7-10] More than improvement in oncohematology, the decreased mortality is attributable to the development of new ICU admission policy, non-invasive diagnostic and therapeutic strategies, refinements in supportive cares (antimicrobial treatments, hematopoietic growth factors, transfusion policies), improved management of organ failure, the use of non-invasive ventilation (NIV), the better cooperation between oncohematologists and intensivists and the development of cancer specialized ICU ("case volume").[11, 12]

Classic predictors of high mortality rates have lost their relevance. Kress reported an unexpectedly low 41% mortality rate in 348 ICU cancer patients,[13] of whom 44% required MV. Neutropenia and autologous BMT, two features previously associated with poor outcome, had no impact on short term mortality. Reassessing new predictors of mortality became crucial, to avoid denial of ICU admission and inadequate end-of-life decisions. In a 237 cancer patients cohort admitted to the ICU between 1990 and 1998, Azoulay [7] et al confirmed that the outcome has improved over time. ICU admission between 1996-1998 and NIV were protective from mortality, whereas Simplified Acute Physiology Score (SAPS II) was associated with a higher mortality. Overall mortality rate was 72%, conventional MV was used first in 80% and NIV in 20%.

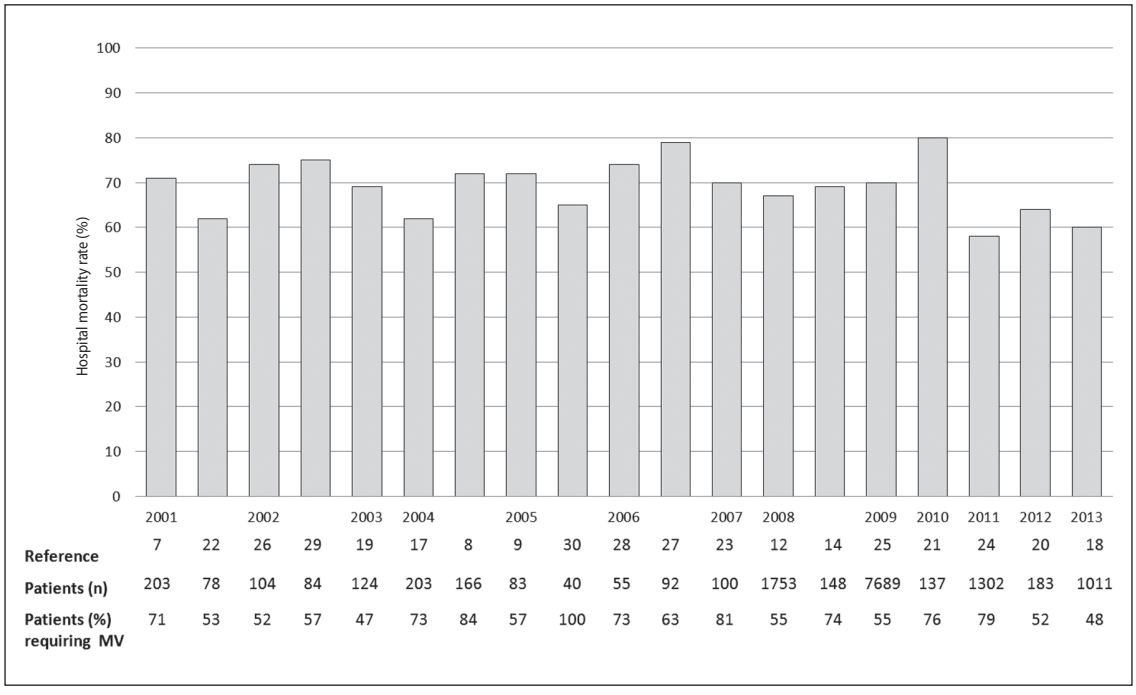

Figure 1.—Hospital mortality rates (%) in studies published over the last decade and conducted in patients with hematological malignancies requiring mechanical ventilation in the intensive care unit.
MV: mechanical ventilation.

Once more, neutropenia and autologous BMT were not associated with mortality.

Improvements keep going. In 2008, hospital mortality rate was 55% in 148 cancer patients with ARF.[14] In a prospective multicenter study, Soares reported a mortality rate of 30% in ICU cancer patients. Mortality was mostly dependent on the severity of organ failures, performance status, and need for MV rather than cancer-related characteristics.[15] These results were confirmed in a 2010 study, where the day-28 mortality rate in ARF cancer patients admitted to the ICU was about 30%.[16] Figure 1 represents hospital mortality rates in studies published over the last decade and conducted in patients with hematological malignancies requiring MV in the ICU.[7-9, 12, 14, 17-30] Mortality has had on upward trend in the last ten years.

ARF in cancer patients: diagnostic strategy and prognostic factors

ARF is defined clinically as tachypnea, recruitment of accessory respiratory muscles or respiratory muscle exhaustion, arterial oxygen saturation lower than 90% on room air, pulmonary infiltrates, and a need for high-concentration face-mask oxygen or for invasive or noninvasive MV. A prompt diagnosis of the ARF etiology allows improving the outcome.[17, 31-34] Figure 2

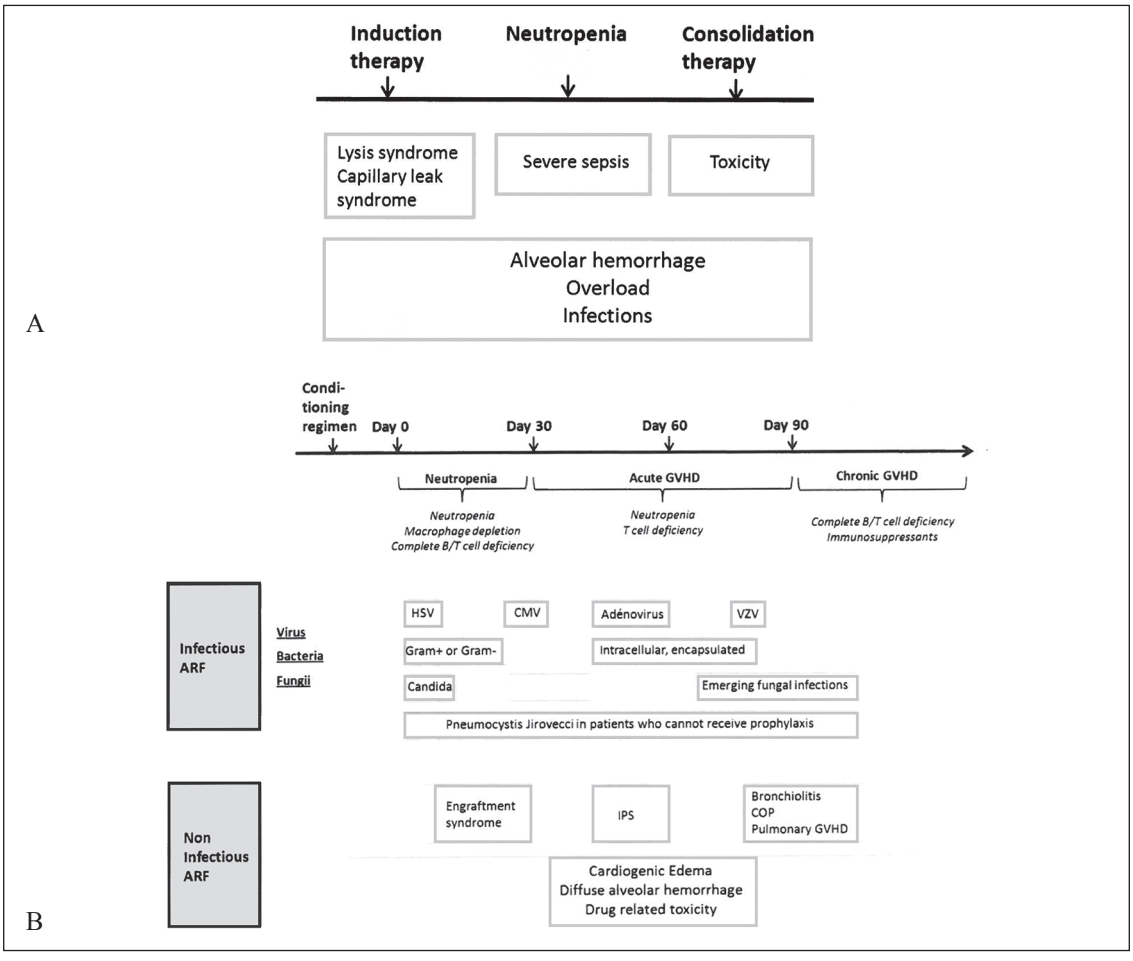

Figure 2.—Causes of acute respiratory failure according to time since (A) the diagnosis of malignancy and since (B) allogenic allogenic hematopoietic stem cell transplantation. Adapted from Azoulay *et al.*[3]
GVHD: graft-versus-host disease; HSV: Herpes Simplex Virus; CMV: Cytomegalovirus; VZV: Varicella Zoster Virus; IPS: idiopathic pulmonary syndrome; COP: cryptogenic organized pneumonia.

presents the main causes of ARF according to time since the diagnosis of malignancy (2A) and since allogenic hematopoietic stem cell transplantation (2B). Unless proven otherwise, ARF in cancer patients must be considered as an infectious emergency, and patients should receive immediate empirical therapy, as soon as acute cardiogenic pulmonary edema is excluded[3,35]. To facilitate the diagnostic strategy, Azoulay has proposed a standardized clinical approach, using 6 factors to select initial antimicrobial treatments and appropriate investigations (Table I).[3] This is the «DIRECT» strategy: Delay since malignancy onset or BMT, pattern of Immune deficiency, Radiographic appearance, clinical Experience and knowledge of the literature, Clinical picture, and findings by high resolution computed Tomodensitometry (HRCT).

Fiber optic bronchoscopy with bronchoalveolar lavage (FB-BAL) was the cornerstone of the diagnostic to look for a lung infection. However it carries risks and its diagnostic and therapeutic efficiency is only 50%. The main risk is respiratory status deterioration requiring MV, which may lead to a 75% mortality rate. In severely hypoxemic cancer patients, 5% to 30% of FB-BAL are associated with adverse events, as hemoptysis and respiratory status deterioration, mostly in BMT recipients.[36] The apparent contradiction between the need to identify the cause of ARF to improve survival and the risk of complications has generated debates about the best diagnostic strategy in hypoxemic cancer patients with ARF, and no specific guidelines have been established for this situation.

The development of new noninvasive diagnostic tools, such as HRCT, nasopharyngeal aspirates sputum and induced sputum examination, serum and urine antigen assays, immunofluorescence tests, polymerase chain reaction tests and multiplex molecular assay, has questioned the place of FB-BAL.[37]

Still, the optimal diagnostic strategy is debated. Two recent multicenter prospective studies evaluated diagnostic bronchoscopy in cancer patients with ARF. In a prospective multicenter observational study with 148 critically ill cancer

Table I.—*Diagnostic strategy in ARF: the «DIRECT approach», a standardized clinical approach.*

1. Delay since malignancy onset or BMT or antibiotics initiation or prophylaxis
   - Non-specific pulmonary complications: alveolar hemorrhage, fluid overload, infection
   - Specific pulmonary complications:
     - Time-specific: malignancy-related lung infiltration (diagnosis, relapse), long term pulmonary toxicity (after treatment)
     - Treatment-specific: diffuse alveolar hemorrhage (allogenic HSCT), bacterial pneumonia and opportunistic infections (high-dose steroids, immunosuppressive treatments, allogenic HSCT)
2. Patterns of Immune deficiency
   - Typical of the underlying malignancy: pneumococcal infection (myeloma, splenectomy), invasive aspergillosis infection (acute leukemia, allogenic HSCT)
   - Typical of the treatments used: Pneumocystis Jiroveccii infection (Fludarabine)
3. Radiographic appearance
   - Unhelpful in patients with febrile neutropenia because of its lack of sensitivity and specificity
4. Clinical Experience and knowledge of the literature
   - Pulmonary Legionella infection in early-stage hairy cell leukemia
   - Lung infiltration with blast cells and pulmonary lysis syndrome in monoblastic leukemia
   - Respiratory symptom exacerbation in patients recovering from neutropenia
5. Clinical picture
   - Limited abnormalities upon auscultation, valuable guidance of extrathoracic abnormalities
   - Fever
   - Time with respiratory symptoms
   - Epidemiological data
6. Findings by the high resolution computed tomodensitometry (HRCT)
   - 90% overall sensitivity and negative predictive value but low specificity and positive predictive value
   - Provide diagnostic orientation rather than a definitive diagnosis and help to select the nature and site of endoscopic sample collection
   - Few cases of specific lesions: halo image during the neutropenic phase and crescent-shaped lucency during neutropenia recovery in patients with pulmonary aspergillosis, and images suggesting alveolar proteinosis or carcinomatosis
   - Identification of a pattern of individual abnormalities: focal or diffuse ground-glass images, nodules in a peribronchial and perivascular, centrilobular, or subpleural distribution, alveolar consolidation, visible interlobular septae, pleural effusions, cavities.

patients with ARF, Azoulay *et al.*[14] showed that a diagnostic strategy without FB-BAL may be as effective as FB-BAL. The cause of ARF was identified in 51% of patients who underwent FB-BAL and in 67% of the other patients. FB-BAL was the only conclusive test in 34% and caused respiratory status deterioration in 49% non-intubated patients, including 36% who required ventilatory support. Hospital mortality was 55% overall, and was not significantly different in the two groups. It suggests that FB-BAL may be unnecessary in 70% of patients and could have been reserved for patients with negative results of noninvasive investigations. Two years later, in a multicenter randomized controlled trial,[16] 219 patients were randomized to early FB-BAL plus noninvasive tests or noninvasive tests only. The need for MV was not significantly greater in the FB-BAL group than in the noninvasive group (35% *vs.* 39%, P=0.62). FB-BAL is safe if performed early, in the ICU, under close monitoring, with NIV support if necessary.[38, 39] The proportion of patients with no diagnosis was not smaller in the noninvasive group (22% *vs.* 20%).

Several studies have identified prognostic factors.[40] Azoulay [17] conducted a prospective 5-years observational study in 203 cancer patients admitted in ICU for ARF. ICU and hospital mortality were 45 and 48%. NIV was used in 39% of patients and conventional MV in 56% with mortality rates of 48% and 75% respectively. By multivariate analysis, factors associated with increased mortality were documented invasive aspergillosis,[41] no definite diagnosis, vasopressors, first line conventional MV, conventional MV after NIV failure and late NIV failure. Hospital mortality was lower in patients with cardiac pulmonary edema.

In another study from Rabbat,[9] 83 patients with acute myeloid leukemia admitted to the ICU, including 82% for ARF, were studied. ICU mortality was 34%. MV was required in 57% of patients. Factors significantly associated with in-ICU mortality were performance status, SAPS II score and need for invasive MV. Age, performance status, AML3 subtype and complete remission were significantly associated with one year survival. The number of organ failures at admission is also strongly independently associated with mortality.[20]

Mechanical ventilation and related outcomes in cancer patients

The need for invasive MV remains a major outcome predictor and is still associated with substantial mortality rates. Table II reports the results of the main studies published over the last decade in cancer patients with ARF, requiring invasive MV (IMV).[8, 9, 12, 14, 16, 17, 20, 21, 24, 42-47]

Impact of patient- and malignancy-related characteristics

Similar mortality rates for hematology and oncology patients requiring MV have been documented recently.[7, 10] Overall hospital mortality rates range from 62% to 80%.[48] Mortality varies according to patient-related characteristics as comorbidities, severity of acute illness, level of ICU support and ICU management. Age per se does not appear to be a major risk factor for short-term mortality. However, aging is associated with a decrease in physiologic adaptation capacity and a higher prevalence of chronic diseases. Comorbidities are poor prognostic factors in general scoring systems like APACHE and SAPS II scores. Performance status is more relevant than age and has a major impact on survival.[10]

After adjustment on other prognostic indicators, the type of malignancy is not associated with short-term outcomes in patients requiring IMV, although worse outcomes have been reported in patients with acute leukemia [8] or lymphoma.[25] On the other hand, higher survival rates were observed in patients with multiple myeloma.[49] Mortality is significantly increased in patients with disease recurrence or progression compared to those with newly diagnosed disease or disease remission status.[29, 44] It should be noted that the literature includes studies from centers with very different admission policies. In recent studies neither the presence of neutropenia nor recent exposure to chemotherapy was associated with an increased risk of death.[10, 50]

However, allogenic BMT recipients requiring IMV did not fully benefit from recent improvements. Short-term mortality rates ranged from 74% to 86%, with an average of 82%.[48] Mor-

TABLE II.—*Mortality rates and prognostic factors in studies published over the last decade (2003-2013) conducted in cancer patients with ARF.*

Author	Design	Patients	Results	Independant prognostic factors
Principi 2004 [46]	Prospective with historical matched controls; single center	N.=34, HM Prophylactive NIV in hematology ward: helmet CPAP *vs.* face mask	Increased success rate and comfort using helmet Hospital mortality 35%	/
Depuydt 2004 [8]	Cohort, retrospective, single center	N.=166, HM	IMV 84% ICU mortality 62%, Hospital mortality 71% NIV failure and switch to ETI: 92% mortality rate	SAPS II score and diagnosis of AML associated with mortality. Female gender, ETI <24 h of ICU admission, recent bacteriema were protective
Azoulay 2004 [17]	Cohort, prospective, single center 5 year observational study	N.=203, HM and solid tumors	ICU mortality 45% Hospital mortality 48% NIV used in 39% patients, ETI in 56%, mortality rates of 48% and 75% respectively	Invasive aspergillosis, no definite diagnosis, vasopressors, NIV failure, first line IVM associated with mortality Congestive heart failure and successful use of NIV were protective
Rabbat 2005 [9]	Cohort, retrospective, single center 9 year observational study	N.=83, AML	IMV 57% ICU mortality 34% One year mortality 49% among patients discharged alive from ICU	SAPS II score and need for IMV associated with mortality Age, PS, AML3 subtype, CR associated with one year survival
Lecuyer 2007 [43]	Prospective study, single center	N.=188, HM and solid tumors, requiring MV, at least one other OF	Hospital survival 22%, 40% in patients with MV 100% mortality in patients requiring MV, vasopressors or RRT after day 3 Mortality: 26% if 1 OF, 55% if 2, 85% if 5, 95% if 6	/
Azoulay 2008 [14]	Prospective observational study, multicenter	N.=148, HM and solid tumors	Hospital mortality 55% ARF diagnosis identified in 50% if FB-BAL and 67% if no FB-BAL	Malignancy characteristics, cause of ARF and need for life-sustaining treatments associated with mortality
Adda 2008 [42]	Retrospective, single center	N.=99, HM	Hospital mortality 41% if NIV success, 79% if NIV failure 54% NIV failure, whom 89% required vasopressors	NIV failure: respiratory rate under NIV, longer delay between admission and NIV first use, need for vasopressors or RRT, ARDS
Lecuyer 2008 [12]	Retrospective study, multicenter	N.=1753, HM	Mortality rate: 40%. 7% if no ventilatory support, 12% if NIV, 67% if IMV	SAPS II, MV, ARDS, shock, vasopressors, coma, RRT, lenght of MV days associated with mortality High volume ICU is protective
Squadrone 2010 [47]	Prospective, randomized study, single center	N.=40, HM, preventive CPAP in hematology ward: oxygen *vs.* oxygen plus CPAP	CPAP decreased the need of ICU admission, ventilatory support, ETI and NIV failure	/
Depuydt 2010 [21]	Retrospective, single center	N.=137, HM NIV *vs.* ETI *vs.* Oxygen only	ICU mortality 71%, 63%, 32% respectively Hospital mortality 75%, 80%, 47% respectively	Severity of illness associated with mortality, but not the type of initial respiratory support
Azoulay 2010 [16]	Randomized controlled trial, multi center	N.=219, HM and solid tumors FB-BAL plus non invasive tests *vs.* non invasive tests only	Need for ETI: 35% *vs.* 39% No ARF diagnosis: 22 *vs.* 20% 28-days mortality: 29% *vs.* 33%	/
Gristina 2011 [24]	5 year retrospective multicenter observational study	N.=1302, HM	Initial ventilatory support: 21% NIV, 79% IMV ICU mortality: 47%, 39% NIV, 50% IMV, Hospital mortality: 56%, 49% NIV, 58% IMV NIV failure: 46%, ICU mortality 78%	Mortality risk factors: ARDS, septic shock, higher SAPS II score NIV failure: SAPS II score, ALI or ARDS at admission
Molina 2012 [45]	Prospective multicenter observational study	N.=300, HM	ICU mortality 69%, 41% NIV, 59% IMV Initial ventilatory support: 44% NIV, 56% IMV NIV failure 26%	Congestive heart failure and initial use of NIV were protective. APACHE II score, shock on admission, allogenic BMT, NIV failure increased mortality. NIV success: age, congestive heart failure, bacteremia
Bird 2012 [20]	Retrospective, 5 year study, single center	N.=199, HM	ICU, hospital and 6-months mortalities: 34%, 46%, 59%. IMV 52%	≥ 2 OF and MV associated with mortality
Mokart 2012 [44]	Prospective study, single center, 6 year period	N.=70, neutropenic cancer patients with ARDS	28 days mortality 63% Most survivors stayed > 3 weeks in the ICU	Lobar ARDS, use of initial antibiotic treatment active on difficult to treat bacteria and first line chemotherapy were associated with good prognosis. Organ dysfunctions, no neutropenia recovery a and vasopressors were associated with ICU mortality

HM: hematological malignancy; NIV: non invasive ventilation; IMV: invasive mechanical ventilation; ETI: endotracheal intubation; ARF: acute respiratory failure; ICU: intensive care unit; AML: acute myeloid leukemia; PS: performance status; CR: complete remission; OF: organ failure; RRT: renal replacement therapy; FB-BAL: fiberoptic bronchoscopy with broncho alveolar lavage; ALI: acute lung injury; ARDS: acute respiratory distress syndrome

tality remains extremely high in ventilated allogeneic BMT recipients with acute severe graft-*versus*-host disease (GVHD) or concomitant hepatic, renal, or cardiovascular dysfunction.[51] The development of reduced intensity conditioning regimens is expected to contribute to improved outcomes in the next years. In contrast, autologous BMT recipients have survival rates close to non-BMT patients, with a 6-months survival rate of 60% in patients requiring MV.[52]

Impact of organ dysfunctions at ICU admission and over the ICU stay

The severity of acute organ dysfunctions correlates directly with short-term mortality.[7, 8, 10, 14] Although severity of illness scores at admission, such as the Sequential Organ Failure Assessment (SOFA) and the Logistic Organ Dysfunction (LOD) scores, are inaccurate for predicting outcomes in HM patients,[53] they have been used as surrogate markers for acute severity and correlate strongly with mortality. Mortality increases with the number of additional failing organs,[12, 17, 43] suggesting an interest of an early ICU admission. The need for additional life-sustaining therapies (such as renal replacement therapy or vasopressors) after a few days on MV are associated with increased mortality.[12, 42] Both the length of ICU admission and duration of MV do not predict survival.

Outcomes also depend on the cause of ARF. The extreme situations are congestive heart failure, which is a protective prognostic factor,[17, 45] and ARDS and invasive aspergillosis, associated with an increased mortality.[17, 44] Additionally, failure to determine the etiology of ARF is independently associated with mortality.[3, 14, 17] Two studies evaluated long term survival and post ICU quality of life with contradictory results,[18, 54] suggesting that long-term expectations should play a larger role during multidisciplinary triage decisions upon ICU referral.

Impact of NIV failure

Mortality rate after NIV failure is about 60%.[24] In contrast, mortality in patients receiving first line invasive ventilation is about 75%. Switching from NIV to IMV has been identified as an independent predictor of mortality.[17, 42] Predictors of NIV failure in cancer patients are short symptom duration at ARF onset, steroid treatment, increasing NIV duration, ARDS, other organ failure requiring vasopressors or renal replacement therapy, failure to identify ARF cause, high SAPS II score, delay in NIV initiation and increasing respiratory rate under NIV.

NIV in cancer patients

In addition to oncohematologic advances and ICU improvements, investigators have attributed the increased survival to the use of NIV.[7, 9] However, only very few studies have demonstrated benefits of NIV in cancer patients. In 2001, a randomized control trial from Hilbert [34] reported several benefits of NIV including improvements in oxygenation parameters, reduced need for endotracheal intubation and its related complications in 52 immunosuppressed patients with ARF, mostly allogenic BMT recipients. The improved survival rates placed NIV as the initial method of choice for ventilatory support for hypoxemic ARF.[55] Concerns were raised about patient's outcomes in the control group in whom intubation was associated with up to 94% mortality.

However, observational studies provided conflicting results (Figure 3).[56] Cohort studies demonstrated that NIV failure (as defined by subsequent need for intubation and mechanical ventilation) was reported in at least half patients [10, 17, 42] and was associated with remarkably high (73-92%) mortality rates.[8] However additional randomized trials are needed to figure out the optimal indications of NIV in this context.[56] Predictive factors of NIV failure have been identified: time from ICU admission to NIV onset, acute respiratory distress syndrome (ARDS), need for vasopressors or renal replacement therapy, a non-rapidly reversible reason or the lack of a definite etiological diagnosis of ARF and malignant airway involvement in solid tumors (Table III).[48]

Results of these studies should be interpreted carefully. Most of them did not control time between ARF onset to NIV implementation, with-

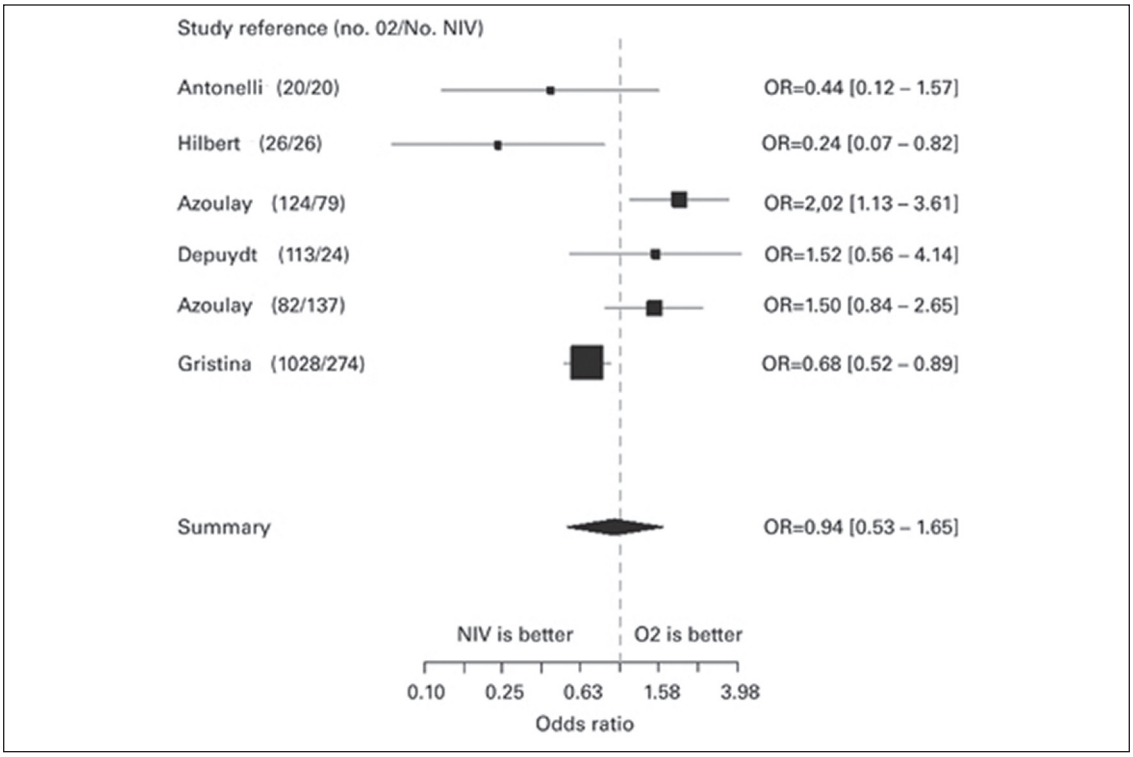

Figure 3.—Outcomes associated with the in-ICU use of non-invasive mechanical ventilation in immunocompromised patients (with BMT permission).[56]

out taking into account ARF etiology and its reversibility, or the presence of associated organ dysfunction at the time of NIV initiation. Moreover, prophylactic and curative NIV were pooled together. Chronic obstructive pulmonary disease and cardiac patients with hypoxemia were included, as were patients with various ARF diagnoses, some of which may respond better to NIV. NIV should be compared with oxygen and early intubation when needed, a therapy that offers nowadays substantial chances of survival.

Table III.—*Predictors of NIPPV failure.*[48]

In general patients
– High severity-of-illness scores (APACHE II≥29, SAPS II≥35)
– Pneumonia
– ARDS
– pH<7.25
– Respiratory rate ≥35 breaths per minute
– PaO_2/FIO_2≤146 (175 for ARDS) after 1 h of NIPPV
– Excessive air leak, lack of tolerance, agitation during NIPPV
In patients with hematological malignancies
– High severity-of-illness scores
– Need for vasopressor therapy
– Need for renal replacement therapy
– ARDS
– Absence of etiologic diagnosis
– Higher respiratory rate under NIPPV
– Longer duration of NIPPV dependency

NIPPV: noninvasive positive-pressure ventilation; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; ARDS: acute respiratory distress syndrome.

Depuydt *et al.*[21] demonstrated in a retrospective cohort study that after adjusting for severity of illness and organ dysfunctions, the initial ventilatory strategy was not associated with improved outcomes. Comparable mortality rates were observed between patients supported initially with NIV and invasive MV (ICU mortality rate 71% *vs.* 63%), which might be explained by a high rate of NIV failure (75%). It provides additional evidence that the expected beneficial effect of NIV in patients with malignancies and ARF may be overestimated.

The efficiency of early or prophylactic NIV (patients with hypoxemia but no respiratory distress),[47, 57] opposite to curative NIV (patients with respiratory distress needing ventilatory support) is not demonstrated. Indeed, there is no

controlled trial of prophylactic NIV in cancer patients and no study has distinguished prophylactic versus curative NIV. Early NIV will need to demonstrate survival benefits and at this stage, studies are warranted.

Another pending question is the best place where to start NIV. A study from Italy has shown that continuous positive airway pressure (CPAP) allowed significant reduction in ICU admission, MV requirement and survival benefits when performed in hematology wards.[47] Wermke *et al.*[58] reported opposite results in a well conducted trial of prophylactic NIV in hematology patients outside the ICU, in the BMT unit. In this study, NIV performed in the wards is ineffective to improve survival in hypoxemic patients. This would be related to the lack of tight monitoring by ICU nurses and availability of intensivists to make adequate and timely decisions. Timing ventilatory support and ICU admission may be hampered by NIV itself, while patients would benefit from early ICU admission and intubation.

The length of NIV is also debated. In the 2000's, Azoulay [17] reported a 100% mortality rate in patients who received NIV for longer than 72 hours. These results may be contradicted by the recent TRIAL-OH study,[18] showing that longer time on life-supporting interventions was no longer associated with worse survival.

At the light of current evidence, what should be the first line ventilatory support for hematologic patients with ARF? Soares made some recommendations about the choice of the appropriate initial ventilatory strategy (Figure 4A).[59] It is crucial to early identify patients with NIV contraindications,[55] and early indicators for increased risk of NIV failure. Knowledge of the baseline determinants of NIV success or failure may help to identify patients who are likely to respond to NIV, and may allow earlier substitution to IMV. If the odds for NIV success are low, the safest approach is immediate intubation. In patients with low risk of failure, NIV should be applied with caution. The response to NIV (in terms of hypoxemia reversal and respiratory rate decline) should be assessed after 1 or 2 hours, and the patient should remain under close monitoring for early signs of NIV failure. If increasing organ failure or persistent ARF is observed over the next few days, switching to IMV should be strongly considered.[10] To our opinion, there is no place for NIV in patients with persistent hypoxemic ARF, advanced respiratory distress, criteria of acute respiratory distress syndrome or associated-organ dysfunction. In numerous studies, these criteria were associated with high risk of NIV and higher mortality.[8, 17, 50, 54] These patients should merely be intubated. Clinicians should always consider whether intubation might be the better choice. Along this time, unanswered questions remain such as palliative NIV, NIV for procedures (BAL), NIV for the non ICU setting (pre-hospital, wards) or post extubation, optimal ventilatory settings and the place for high flow oxygen in these patients.

Practical guidelines

Merits of admitting cancer patients in ICU have been strongly debated [60, 61] in patients requiring life sustaining interventions (mechanical ventilation, vasopressors, renal replacement therapy).[62] Recent data suggest that an increased number of cancer patients benefit from intensive care support, with dramatically decrease mortality rates and long term benefits. Intensivists should not be reluctant anymore in admitting cancer patients and providing invasive MV.[63]

ICU admission criteria are very heterogeneous and not clearly evaluated. As soon as classic prognosis factors as age, malignancy, allo-BMT or neutropenia are not relevant anymore, decisions should not be made on these criteria. In 2005, in a prospective study [64] evaluating non ICU admitted patients, 26% patients were considered too sick to benefit, and 23% patients too well to benefit from the ICU. 20% of the too well patients died before day 30, and 25% of the too sick patients were still alive at day 30. Both the excess mortality in too well patients later admitted to the ICU and the relatively good survival in too sick patients suggest the need for a broader admission policy.[65] The goal of ICU admission selection is to avoid depriving life support to patients who can benefit from an ICU management, without unreasonable therapeutic obstinacy, while respecting patient's values, wishes and life expectancy. The therapeutic plan

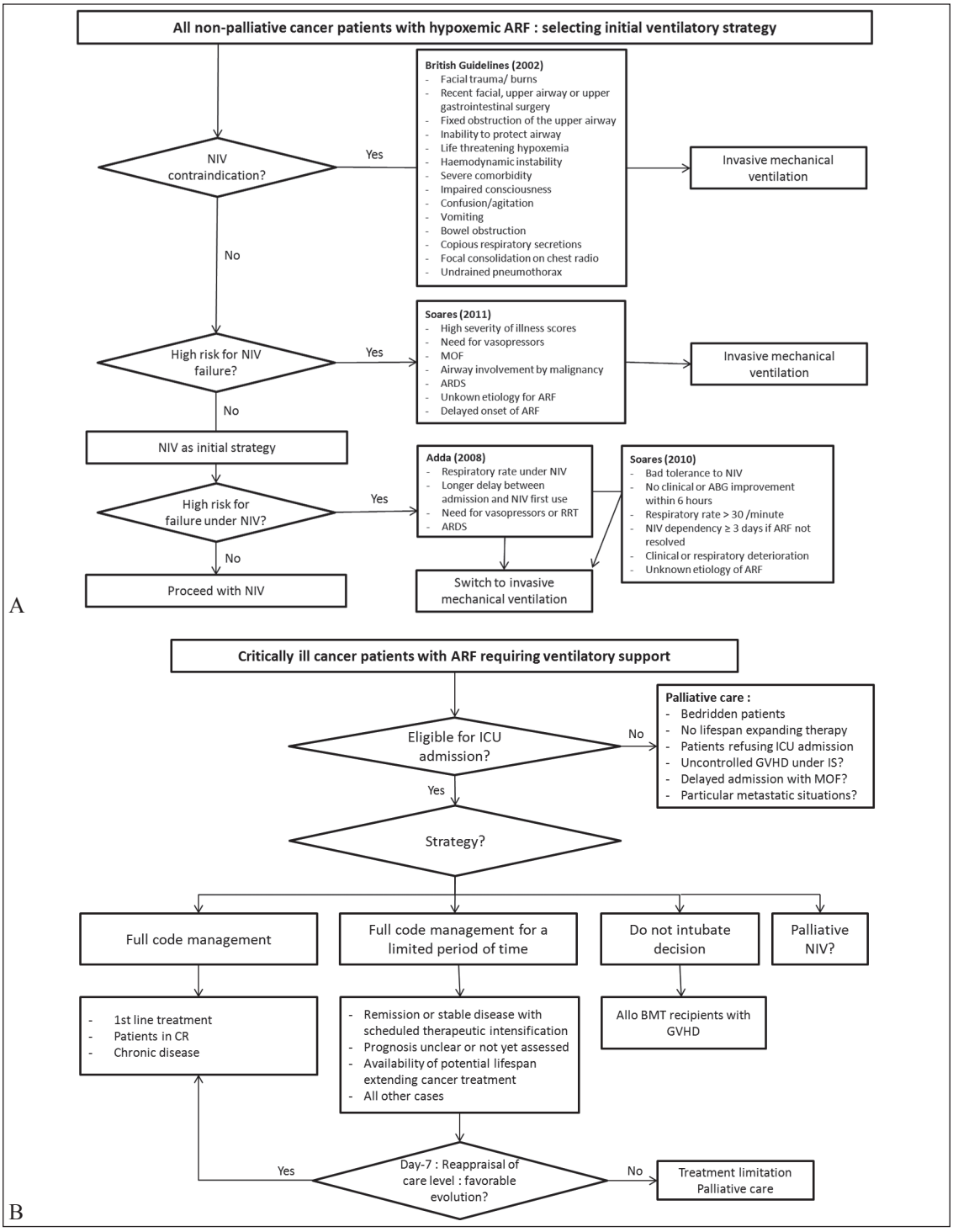

Figure 4.—Practical recommendations (A) to select initial ventilatory strategy in patients with maligancies and hypoxemic ARF (adapted from Soares) [59] and (B) for patients requiring ICU admission for ventilatory support.
ARF: acute respiratory failure; MOF: multi organ failure; NIV: Non Invasive Ventilation; RRT: renal replacement therapy; ARDS: acute respiratory distress syndrome; ABG: arterial blood gas analysis; ICU: intensive care unit; BMT: bone marrow transplantation; GVHD: graft versus host disease; IS: immunosuppressive therapy; CR: complete remission.

must be early clarified with patients, relatives, oncologists and hematologists.

Patients ineligible to ICU admission for MV

In some situations, it is uncontroversial that escalating care is inappropriate. Patients are ineligible for MV in 4 different contexts: 1) When a competent patient refuses it, directly or through written advanced directives; 2) when a patient is unresponsive to chemotherapy, with terminal and irreversible illness facing imminent death [24] and requires comfort care, because survival rates in ICU is disastrous;[66, 67] 3) when a patient is bedridden or severely dependent; 4) when patients have a terminal condition. In other situations with extremely poor prognosis such as allo-BMT recipients with an uncontrolled GVHD under immunosuppressive treatments,[51] patients lately admitted to the ICU with multiorgan failures,[43] particular metastatic situations as pulmonary lymphangitis, carcinomatous meningitis and metastatic bone marrow infiltration, MV should be perceived as a non-beneficial therapy. In these cases, ICU admission for MV should not automatically be refused, but the decision is a case by case multidisciplinary discussion. Figure 4B suggests practical recommendations.

Patients eligible for ICU admission: different ventilatory strategies contexts

Full ICU management with no therapeutic limitations

Cancer patients admitted to the ICU should have a curative therapeutic project, and everything that can be done has to be done in the ICU, including chemotherapy, vasopressors, renal replacement and mechanical ventilation (IMV or NIV). The goal is to cure the acute life threatening complication and obtain the underlying cancer cured. The most frequent patients concerned by this full ICU management are first line treatment patients or chronic evolution cancers. The ICU management should be similar with patients with no underlying malignancies. Concerning BMT recipients, a full ICU management should be initiated with no hesitation in three particular cases: in the first 4 weeks following BMT (before GVHD), in controlled GVHD situations, and when MV is required for central neural complications (convulsive status epilepticus or reversible encephalopathy).

Full code without intensity limitations for a limited time period

For other patients, selection criteria are not reliable.[43] The decision not to admit a patient to the ICU could be a loss of chance. An alternative of ICU admission rejection is to initiate a full ICU management without intensity limitations, for a limited time period. Treatment-limitation decisions are discussed according to the evolution. More than severity factors at admission, the evolution of organ failures between admission and day 3 are the main prognostic factors. Initiation of MV and aggravation of multi organ failures after 3 days are strongly correlated with mortality.[7, 60] In the first description of the ICU trial in 2003, all patients who required initiation of life-sustaining interventions after day 3 died. Azoulay has proposed a full intensive care management up to day 3 or 5, followed by a daily reassessment of organ dysfunctions and factors associated with mortality. In patients with no improvements, treatments should not be escalated. Objectives have to be discussed by a multidisciplinary team to eventually initiate a palliative process. End-of-life decisions should not be taken before day 3.

ICU admission for palliative NIV

NIV is increasingly used as a palliative strategy when endotracheal ventilation is deemed inappropriate, particularly in patients with end-stage chronic obstructive pulmonary disease, heart failure or degenerative neurological diseases.[68] In cancer patients, benefits seem dismal. Palliative NIV can either be administered to offer a chance for survival or as comfort care to alleviate the symptoms of respiratory distress in dying patients [69] while preserving patients communication. It is still controversial to consider that the ICU is the best place to offer NIV as a

palliative tool or to state that the ICU is a good place to die.

A recent prospective observational cohort study [70] reported outcomes after NIV in patients with a do-not-intubate (DNI) order compared with patients receiving NIV with no treatment-limitation decisions (TLD) in 54 ICUs in France and Belgium. One-fifth (of 708 patients) of critically ill patients receiving NIV for ARF had DNI decisions. The day-90 data in the DNI group indicate that NIV prolonged life, as opposed to merely prolonging the dying process. Furthermore, NIV with DNI decisions was not associated with increased symptoms of anxiety, depression, or stress among relatives, compared to NIV without TLDs. These results support the use of NIV in the ICU for patients with DNI decisions.

Early ICU admission?

In a prospective randomized trial including 219 cancer patients with ARF, Mokart reported an increased mortality associated with a delayed ICU admission.[71] After adjustment on the LOD score at admission, only time between respiratory symptoms onset and ICU admission >2 days and the LOD score were independently associated with day-28 mortality. Determinants of death include both factors non amenable to changes, and delay in the ARF management. It suggests that an early ICU management may translate into better survival. Moreover, early admission allows the use of noninvasive diagnostic strategies and patients admission with fewer organ failures. In patients with newly diagnosed high-risk AML, direct admission to the ICU is associated with improved outcomes in patients with physiological disturbances but no organ dysfunction.[72] Oncohematologists should collaborate with intensivists upstream, to evaluate the best moment for admission in ICU.[73]

Conclusions

Improvements in both intensive care and oncohematologic management have modified ARF diagnostic and therapeutic management. The diagnostic demarche and the choice of the appropriate initial ventilatory strategy are pivotal. Unanswered questions remain on ICU admission policy. The admission policies have to be prospectively evaluated. The best moment when patients should be admitted remains unclear, as the best moment to interrupt curative intensive therapies. Observational or interventional studies are warranted to address these burning issues.

Key messages

— Despite an improvement in the last decade, mortality associated with invasive mechanical ventilation remains high.

— Non-invasive mechanical in that setting remains controversial and could be considered only for patients without associated organ failure nor ARDS. Tight monitoring is therefore recommended to switch to mechanical ventilation if needed.

— Mechanical ventilation in cancer patient would be included in a global strategy according to the prognosis of underlying disease.

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