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Guest Editorial

Differentiation syndrome in patients with acute promyelocytic leukemia

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Differentiation syndrome (DS), formerly known as retinoic acid syndrome, is the main life threatening complication of differentiating agents (all-trans retinoic acid [ATRA] or arsenic trioxide [ATO]) in patients with acute promyelocytic leukemia (APL).[1] This complication typically occurs during induction therapy with differentiating agents while leukemic blast massively present, but it never take place during consolidation or maintenance therapy for APL. This syndrome is characterized by unexplained fever, acute respiratory distress with interstitial pulmonary infiltrates, and/or a vascular capillary leak leading to acute renal failure.[2]

Differentiation syndrome (DS), formerly known as retinoic acid syndrome, is the main trans retinoic acid [ATRA] or arsenic trioxide [ATO]) in patients with acute promyelocytic leukemia (APL). The differentiation of leukemic blasts and promyelocytes induced by ATRA and/or ATO may lead to cellular migration, endothelial activation, and release of interleukins and vascular factors responsible of tissue damage.[3] Roughly one quarter of patients with APL undergoing induction therapy will develop the DS, characterized by unexplained fever, acute respiratory distress with vascular capillary leak syndrome leading to acute renal failure. Although the development of the DS, particularly of the severe form, is still associated with a significant increase in morbidity and mortality during induction, the early administration of highdose dexamethasone at the onset of the first symptoms seems likely to have dramatically reduced the mortality rate of this complication.[4]

Although a "cytokine storm" has been described coinciding with differentiation of blasts, the underlying etiopathogenic mechanisms of this syndrome remain partially unknown. The diagnosis of the DS is mainly based on clinical and radiological features in the context of induction therapy of APL with differentiating agents, and it usually requires the exclusion of alternative causes that could explain the signs and symptoms of the syndrome.[5]

Early therapeutic or presemptive interventions to counteract the DS using intravenous corticoids and other supportive measures should be instituted at the onset of the first suggestive signs and symptoms and before exclusion of other possible causes.[6]

Diagnosis of the DS. The first description of DS by Frankel et al, was based on the observation of a distinctive clinical syndrome in 9 out of 35 APL patients who were treated with ATRA alone for induction therapy.[1] All of them had developed a variety of signs and symptoms characterized primarily by fever, respiratory distress, weight gain, and a chest radiograph showing pleural effusion and pulmonary infiltrates. Other clinical features, such as peripheral edema, unexplained hypotension, renal insufficiency, hyperbilirubinemia, and pericardial effusion, were also associated with the syndrome with variable frequency. Although most subsequent studies reporting the incidence and clinical characteristics of DS in APL refer

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to Frankel's definition, it must be noted that in several representative reports there is a variable interpretation of the original description.[1]

The PETHEMA group has recently reported the incidence and characteristics of DS in two large series 9,10 of patients undergoing induction therapy with the AIDA regimen using the same definition criteria, which were based on the presence of at least two of the following signs and symptoms: dyspnea, unexplained fever, weight gain greater than 5 kg, unexplained hypotension, acute renal failure, and, particularly, a chest radiograph demonstrating pulmonary infiltrates or pleuropericardial effusion. No single sign or symptom was considered sufficient to diagnose the syndrome, and any alternative cause explaining the clinical clinical features should be ruled out. For some authors, patients with an alternative cause explaining the syndrome have been classified as indeterminate DS, with a frequency varying from 4% to 19%, while others have used the term indeterminate DS for patients manifesting only a partial symptom complex (i.e., patients with less than 4 clinical criteria of DS). In the PETHEMA studies, a severity gradation of the DS for predicting outcomes was established, using the terms moderate and severe DS according to the number of clinical criteria fulfilled. Thus, patients with 4 or more of the above signs and symptoms were classified as having severe DS, while those with less than 4 signs or symptoms were considered to have moderate DS.[5,7]

The diagnosis of the DS is mostly based on the above defined clinical and radiological criteria and supported by the striking response to early therapy with intravenous corticosteroids. The use of invasive diagnostic techniques, such as bronchoscopy and bronchoalveolar lavage or lung biopsy, is not usually required in patients with suspected DS and respiratory distress with lung infiltrates. Nevertheless, when the clinical course is not satisfactory despite receiving appropriate therapy, or when the patient needs orotracheal intubation for mechanical ventilation, the bronchoscopy and bronchoalveolar lavage could be useful to exclude a pulmonary haemorrhage or an infection causing the respiratory distress. Lung biopsy is usually contraindicated in patients with DS that frequently shows concomitant severe thrombocytopenia and coagulation disorders leading to an extremely high risk of bleeding complications. When performed, in life or in postmortem examination, the major histologic findings of lung biopsies are interstitial infiltration with maturing granulocytic cells, diffuse alveolar damage, intraalveolar haemorrhage, and small vessels inflammation.[3,5,8]

Conclusions Roughly one quarter of patients with APL undergoing induction therapy will develop DS. The early administration of high-dose dexamethasone at the onset of the first signs or symptoms of DS is crucial, since it appears to dramatically reduce mortality of this complication. The etiopathogenic mechanisms of this life-threatening complication are complex and remain partially unknown. Specific biological therapies to counteract the syndrome are still not available. Randomized studies are required to ascertain whether or not the use of corticosteroid prophylaxis is advantageous, particularly taking into account that infectious mortality is not apparently increased when prednisone prophylaxis is used. Risk adapted prophylactic and therapeutic strategies based on the adverse risk factors for development of severe DS (e.g., WBC counts > 5 × 109 /L or abnormal levels of serum creatinine) require further research.

1. Conflict of Interest

The authors declare they have no conflict of interest.

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