Featured Article

End of life care in hematology: still a challenging concern

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Abstract: The majority of patients with hematological malignancies (HM) may experience troublesome symptoms and complicating clinical syndromes throughout all phases of disease. Therefore, among the current concepts concerning the comprehensive management of hematological patients, palliative care should exert a more ever expanding role, in particular in the advanced phases of disease, as there are special clinical needs (such as blood transfusions and anti-infective treatments), presented by this peculiar category of cancer patients. However, reported experiences on advanced HM patients claimed a too intensive level of medical care during the last week of life for which the needs of future and collaborative researches in order to set a proper allocation of medical resources and the optimal end-of-life care in the hematologic setting are highly awaited. Indeed, the most important aspect of caring for these suffering patients is to ameliorate or restore their quality of life (QoL) though a highly humanized approach, whereas technological and pharmacological measures should be limited enough to control the symptoms burden and the several kinds of sufferance that may complicate the final phase of disease course.

Keywords: End of life care; palliative care; hematological malignancies (HM); anemia; infections; pain; palliative sedation; transfusion

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The majority of patients with hematological malignancies (HM) may experience troublesome symptoms and complicating clinical syndromes throughout all phases of disease. Therefore, among the current concepts concerning the comprehensive management of HM patients, palliative care should exert a more ever expanding role (1), in particular in the advanced phases of disease. Indeed, the most important aspect of caring for these suffering patients is to ameliorate or restore their quality of life (QoL) though a highly humanized approach, whereas technological and pharmacological measures should be limited enough to control the symptoms burden and the several kinds of sufferance that may complicate the final phase of disease course. However, despite the important implications in terms of allocation of medical resources, the effectiveness of care as well as the choice of most appropriate place of the last care and demise for suffering patients to be close to the death, the management of HM patients in the last week of life has been addressed by very few specific studies (2-4). In the light of these premises, the recently published paper by Cheng and colleagues, dealing with a retrospective analysis on the level of medical care provided in hospice to 25 HM patients during the final week of their life (5), represents an important contribution on this topic. The authors reported that during the last week of life, 85.7% of patients had blood sampling whereas 14.3% of them were on total parenteral nutrition. Given the reduced blood counts, 23.8% of patients received granulocyte colony-stimulating factor (G-CSF) for neutropenia, whereas one-third of them received transfusion of red blood cell (RBC) units and nearly half of them received platelet concentrates. In addition, almost 90% of patients received antibiotics. An important and valuable finding outlined by the authors is represented by the good and fruitful collaboration between hematology and palliative care, which, in their experience, allowed for a successful transition of hematologic cancer patients into hospice unit in their terminal phase of illness. Despite this promising and significant finding, however, the level of medical care, during the last week of life of their patients was

too intensive, for which the authors claimed the need of future and collaborative researches in order to set a proper allocation of medical resources and the optimal end-of-life care in the hematologic setting (5).

HM patients in advanced phase of disease may suffer from a troublesome symptom burden which is above all represented by the consequences (anemia, thrombocytopenia and neutropenia) and clinical complications (fatigue, dyspnea, infections, bleeding and so on) of bone marrow failure; moreover, coagulation disturbances and several kind of pain syndromes may be also present (1,6-10); lastly, advanced HM patients may complain all others kinds of sufferance presented in general by cancer population in the last phase of disease course, including the loss of autonomy and several forms of disability (11) and their implications (12), as there are special clinical needs (such as blood transfusions and anti-infective treatments), presented by this peculiar category of cancer patients.

Therefore, as it has been recently outlined (4), palliative situations in HM setting remains a major challenge as there are special clinical needs, such as transfusions and the infectious complications requiring broad anti-infective treatments, presented by this peculiar category of cancer patients such as those suffering from HM (1) which are treated for the most time of their clinical course with curative or, at least, with disease containing intents. This aspect has been further accentuated by the availability of new drugs with better tolerability profile and limited toxicity; noteworthy, most HM may retain, at least, a partially limited sensitivity to antineoplastic treatments or adjuvants measures, such as high-dose steroids, for which their application, at least in selected cases, may be justified also in advanced phase of disease with disease-containing and symptoms relief intents. Moreover, the treatment approach applied with curative intent maybe not appropriate for HM patients in palliative situations, may resulting this aspect resulting in futile over medicalization and inappropriate therapeutic aggressiveness in the last days of life (2-5). Therefore, the close relationship between the treating hematologist and patients, who often have a relatively long history of disease and may represent an obstacle to the appropriate transition from a the "curative" setting typically represented by the hematologic ward to the palliative care (4), which can be provided in hospice and/or at home (1,13,14). At the same time, although efforts to provide a scoring system to estimate survival in advanced HM have been provided (4), no formal definitions or diagnosis of terminal disease may be applied in this setting. With this regard, a HM patient may be considered as being terminally ill as the result of the physician's perception, the inefficacy of causal treatments and the patient's symptoms burden. However, in many cases, the illness trajectory may be not clearly defined, being and the disease progression variable in time and a not linear process as result of the partially residual response to causal treatments which may improve the patient's subjective status and symptom burden (15). Therefore, the transition from causal therapies to a holistic model of end of life care focused exclusively to the dying person and not on the disease, with the ultimate goal of preserving as much as possible her/his dignity and QoL, though the relief of physical symptoms and psychological distress, and support to her/his family, may be a challenge. With this regard, every effort to ensure the continuity of care and a frank and empathetic communication between physician, patient and family should be provided. However, once this transition has occurred, the management of palliative HM patients should be carefully reconsidered, avoiding to give unnecessary and expensive measures and, on the other hand, to do provide beneficial symptoms relief by the application of appropriate treatments; in this view, in the clinical decision-making, a balance between the ethical principle of patient's right and protection by arbitrary decision to withdraw effective medical interventions just because expensive and the social need for an equitable allocation of resources is often a matter of debate (16). In this view, some aspects of intensive treatments reported by Cheng and colleagues in end of life care of HM patients deserve a more detailed discussion. Anemia, pain, infection and bleeding are the complaints that most often need to be palliated in the end life of HM patients. The administration of blood components to HM patients should be assessed on a case by case basis by evaluating the patient and not the blood counts; with this regard, the beneficial effects of RBC transfusions in HM patients with symptomatic anemia should be safeguarded; focusing the clinical attention to the individual sufferance and not to anemia itself (1,16). In thrombocytopenic patients with HM in advanced course, given the chronic and unrecoverable outcome of thrombocytopenia and the rapidly development of refractoriness to platelet concentrates transfusions, this measure should be used in the event of significantly actual bleeding (8,16,17); with this regard, the infusion of platelet concentrates can be considered an appropriate and proportionate measure to control potentially distressing and devastating manifestations for the patient and her/his family (8,16,17). On the other hand, platelet

transfusions have not a role as bleeding prophylaxis in thrombocytopenic patients given the short duration of circulating platelets after their infusion and the refractoriness to them which may develops even after only a few administrations (8,17). However, massive hemorrhages in thrombocytopenic patients with HM are quite rare and other alternative and inexpensive measures, although not proven in controlled studies, may have a role as bleeding prophylaxis in the setting of advanced HM. In an Italian home care program for patients with advanced HM, out of 469 referrals, 217 (46%) presented severe thrombocytopenia (platelet count $<20\times10^9$/L for at least one day). Out of the 217 thrombocytopenic patients, 123 (26%) experienced a bleeding complication; the overall number of hemorrhagic episodes was 232 (49%) with a median number of two episodes per patient. Patients with a platelet count lower than 20×10^9/L or with a diagnosis of acute leukemia or in blast crisis of myeloprolypherative disorders showed a significant higher incidence of hemorrhages than other patients. Resolution of bleeding at home was obtained in 206 (88%) of the 232 episodes; platelet units were transfused at home in 188 (81%) cases. Bleeding was the cause of hospitalization only in four cases; bleeding complications (11 brain hemorrhage, 2 hematemesis, 3 hemoptysis and 10 melena) were the cause of death in 26 (6%) of patients. During the home care program, prednisone (0.1-0.15 mg/kg/day bid or more if prescribed for other clinical reasons) and tranexamic acid (100 mg/kg/day tid) but not prophylactic platelet transfusions were given as bleeding prophylaxis if patients were asymptomatic or presenting with minor bleeding such as petechiae and ecchymoses. In the event of any bleeding episode, patients received treatment with local hemostatic agents, if applicable, such as topical tranexamic acid and sucralfate. If no cessation of bleeding, tranexamic acid (80 mg/kg/24 hours) on continuous IV infusion and platelet concentrates (single donor, if available, or random concentrates) were administered. In case of uncontrolled massive haemorrhage, palliative sedation was offered to bleeding patients perceived to be close to death for which resuscitation was not appropriate (1,8,13,17). Therefore, although never studied in a prospective manner, at present, in thrombocytopenic patients with advanced HM, a prophylactic approach based on tranexamic acid plus prednisone low doses, as usually used by hematologistsists in routine clinical practice (8), seems reasonable and recommendable (8,17). Advanced HM patients are often immunodeficient and neutropenic for which they are at high risk of infections; in addition, infections represent the major ultimate cause of death in this setting. However, in spite of the magnitude of these problems, the management of infections occurring in advanced and end life phases of HM diseases has been specifically addressed only by few studies (7-18). In the study by Girmenia and colleagues (7), the authors conducted a retrospective analysis on 151 advanced HM patients managed at home reporting a total of 109 febrile episodes in 70 (46%) of them. Fever was of unknown origin (FUO) in 51% of cases; microbiologically and clinically documented infections accounted for 26% and 23% of febrile episodes, respectively. Pneumonia and bronchitis are the top two amenable infections. The performance status and the neutrophil count significantly affected the incidence of infections. Streptococcus pneumonia, Staphylococcus aureus, and Escherichia coli were the bacterial agents most commonly involved. Relatively inexpensive antibiotic approaches, such as oral ciprofloxacin in patients not neutropenic and once-daily intravenous ceftriaxone plus amikacin in neutropenic patients, were shown to be effective and suitable for empirical home antibacterial treatment, allowing the resolution of 81% of febrile episodes. Infections were fatal in 19.3% of cases. The home care approach resulted clinically effective and has been suggested as cost saving, improving in the patient's QoL, and avoiding the risk of useless hospitalization (7). In general, antibiotic therapy should be aimed at palliation of symptoms from infection and, in this view, the choice must still be made on a case-by-case focusing on the patient's symptoms and sufferance rather than the infection itself (7,18,19); however, considering the potential benefits on the QoL by the treatment of symptomatic infections, such as urinary infections (18), cellulitis, pneumonia (7) and so on, a proportionate antibiotic therapy seem an acceptable and recommendable choice in this setting (7). Therefore, the best management and the decision-making process regarding treatment versus no treatment of an infection can be complex in terminally ill patients and needs to be individualized (19) being the symptom control the primary goal of the management; with this regard, the role of antimicrobial agent in symptoms palliation in the setting of advanced HM deserves future and specifically designed prospective investigations. As further comment to the data reported by Cheng and colleagues (5), we would emphasize that the use of G-CSF outside the curative setting is not justified (20) and it seems a futile treatment in the advanced HM given that neutropenia is almost always disease related in nature and as such unrecoverable. Other than specific blood-related complaints,

advanced HM patients may experience all other physical, psychological and spiritual problems afflicting the general cancer population. In the terminal phase of HM pain is a common issue (9) as well as its control is often inadequately achieved (21), above all in particular situations, such as in frail patients or in those presenting comorbidities (22). Moreover, difficult to treat pain syndromes, such as those of neuropatic and incident origins, prevailed in particular category of patients, such as those affected by multiple myeloma (23,24). Epidemiological and clinical features of pain syndromes in the advanced hematological population have been detailed in a study which included 469 consecutive referrals to an Italian home care program; 244/469 (52%) patients complained for at least one kind of pain. So that, overall 284 pain syndromes were diagnosed as due to BM expansion in 33% of cases, lymphadenopathy and visceral involvement in 18%, osteolysis in 16%, OM in 11%, herpes zoster neuralgia in 6%, meningeal disease in 5%, and other causes in 11%. The type of pain was classified as follows: deep somatic in 56%, superficial somatic in 15%, visceral in 14%, mixed in 8% and neuropathic in 7% of pain syndromes. In conclusion, the great advances observed in hematology in last decades did not alter the ultimate prognosis of the majority of HM. In the absence of studies on the quality of death, collaborative research between hematologists and palliative care specialist should be essential in order to define shared guidelines on the time to referral and to the necessary and appropriate modifications of the treatments that should be reconsidered at the time of transition between the setting of causal and disease-modifying treatments and the end of life care, which management should be based on the symptoms control and include non-invasive and highly humanized measures, such as psychological and spiritual support and other forms of intervention focusing on the dying person and her/his family rather than the disease itself, being it no longer treatable for the purpose of a significant increase in the survival for which some unjustified and futile invasive interventions could aggravate the already deteriorated patient's QoL. In some experience, the development of comprehensive programs for the management of HM, based on multidisciplinary home care services coordinated with hematological wards and hospice, have allowed, trough the ensuring of continuity of care, the increased patient's and family satisfaction, the reduction of time spent in the hospital in the last days of life (1,7-10,13,14). The "technological imperative" (25) and the prevalence of invasive medical interventions in the setting of end of life care for HM patients do represent one of the most important reasons for which the majority of them continues to die in hospital, often in wards for acutely ill patients and as such unsuitable for terminally ill and dying individuals; for these patients, the overt goal should be a peaceful demise, ideally accomplished at home or in hospice by a skilled palliative care team working in close collaboration with hematologists.

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References

1. Niscola P, Scaramucci L, Giovannini M, et al. Palliative Care in malignant hematology: an overview. Haema 2005;8:297-315.
2. Stalfelt AM, Brodin H, Pettersson S, et al. The final phase in acute myeloid leukaemia (AML). A study on bleeding, infection and pain. Leuk Res 2003;27:481-8.
3. Bauduer F, Capdupuy C, Renoux M. Characteristics of deaths in a department of oncohaematology within a general hospital. A study of 81 cases. Support Care Cancer 2000;8:302-6.
4. Kripp M, Willer A, Schmidt C, et al. Patients with malignant hematological disorders treated on a palliative care unit: prognostic impact of clinical factors. Ann Hematol 2014;93:317-25.
5. Cheng BH, Sham MM, Chan KY, et al. Intensive Palliative Care for Patients With Hematological Cancer Dying in Hospice: Analysis of the Level of Medical Care in the Final Week of Life. Am J Hosp Palliat Care 2013. [Epub ahead of print].
6. Efficace F, Cartoni C, Niscola P, et al. Predicting survival in advanced hematologic malignancies: do patient-reported symptoms matter? Eur J Haematol 2012;89:410-6.
7. Girmenia C, Moleti ML, Cartoni C, et al. Management of infective complications in patients with advanced hematologic malignancies in home care. Leukemia 1997;11:1807-12.
8. Cartoni C, Niscola P, Breccia M, et al. Hemorrhagic complications in patients with advanced hematological malignancies followed at home: an Italian experience. Leuk Lymphoma 2009;50:387-91.
9. Niscola P, Cartoni C, Romani C, et al. Epidemiology, features and outcome of pain in patients with advanced hematological malignancies followed in a home care program: an Italian survey. Ann Hematol 2007;86:671-6.

10. Tendas A, Niscola P, Ales M, et al. Disability and physical rehabilitation in patients with advanced hematological malignancies followed in a home care program. Support Care Cancer 2009;17:1559-60.
11. Tendas A, Cupelli L, Trawinska M, et al. Disability effect on survival of home care onco-hematological patients. Haematologica 2013;98:57-8, abstract 119.
12. Tendas A, Cupelli L, Trawinska MM, et al. Accidental falls in home care hematological patients. Support Care Cancer 2013;21:2087-9.
13. Niscola P, de Fabritiis P, Cartoni C, et al. Home care management of patients affected by hematologic malignancies: a review. Haematologica 2006;91:1523-9.
14. Niscola P, Tendas A, Giovannini M, et al. Transfusions at home in patients with myelodysplastic syndromes. Leuk Res 2012;36:684-8.
15. Surbone A. There is no dividing line. Crit Rev Oncol Hematol 2003;46:1-3.
16. Smith LB, Cooling L, Davenport R. How do I allocate blood products at the end of life? An ethical analysis with suggested guidelines. Transfusion 2013;53:696-700.
17. Pereira J, Phan T. Management of bleeding in patients with advanced cancer. Oncologist 2004;9:561-70.
18. Rosenberg JH, Albrecht JS, Fromme EK, et al. Antimicrobial use for symptom management in patients receiving hospice and palliative care: a systematic review. J Palliat Med 2013;16:1568-74.
19. Tendas A, Cupelli L, Trawinska MM, et al. Antifungal Drugs in the Management of Hematological Diseases in a Home Care Program. Home Health Care Management & Practice 2013;25:247-9.
20. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187-205.
21. Niscola P, Tendas A, Scaramucci L, et al. Pain in malignant hematology. Expert Rev Hematol 2011;4:81-93.
22. Niscola P, Tendas A, Giovannini M, et al. Pain management in hematological patients with major organ dysfunctions and comorbid illnesses. Cardiovasc Hematol Agents Med Chem 2012;10:135-47.
23. Tendas A, Niscola P, Giovannini M, et al. Epidemiology and pathogenesis of incident pain-related disability in malignant hematology: an Italian survey. Ann Hematol 2011;90:719-20.
24. Niscola P, Scaramucci L, Romani C, et al. Pain management in multiple myeloma. Expert Rev Anticancer Ther 2010;10:415-25.
25. McGrath P. End-of-life care for hematological malignancies: the 'technological imperative' and palliative care. J Palliat Care2002;18:39-47.

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