General Practice

Hudson et al., J Gen Practice 2016, 4:2
http://dx.doi.org/10.4172/2329-9126.1000245

Research Article Open Access

Hyponatremia: A Potential Prognostic Biomarker in Malignant Pleural Mesothelioma?

Hudson Z[1], **Grosso F**[2], **Charles Comins**[1] **and Alfredo Addeo**[1*]

[1]*Bristol Cancer Centre, Oncology Department, UK*

[2]*SS Antonio e Biagio Hospital Alessandria, UK*

[*]**Corresponding author:** Alfredo Addeo, Bristol Cancer Centre, Oncology Department, UK, Tel: 0117 342 1862; E-mail: alfredo.addeo@uhbristol.ns.uk

Received date: March 15, 2016; **Accessed date:** April 21, 2016; **Published date:** April 29, 2016

Abstract

Objectives

Malignant pleural mesothelioma (MPM) remains an incurable and with very poor outcome cancer. The median survival is 12 months with first line therapy; a median survival of 24 months at best when treated with multimodal approach (both neoadjuvant chemotherapy and surgery with or without radiation therapy or postoperative chemotherapy). Identifying a possible prognostic marker would seem imperative. Several studies, all with limited numbers of patients, have tried to find a possible valid and reliable prognostic marker. Univariate and multivariate analyses had been performed, yet the majority of the findings remain invalidated in other MPM populations.

It has been recently shown that a reduction in serum sodium could have negative effects on hospitalization length, quality of life and prognosis in cancer patients.

Materials and methods

We therefore performed a retrospective single institute analysis to assess and possibly confirm the prognostic role of hyponatremia in MPM.

Results

The OS and the PFS in the hyponatremia group are inferior to the patients who had normal serum sodium level throughout the treatment. None of our patients presented with hyponatremia, but having sodium serum level <130 at some point during chemotherapy was a strong indicator of short PFS and a negative prognostic factor. The findings were similar in first and second line setting.

Conclusion

Further prospective, well designed trial, are warranted to better explore the impact of sodium correction on the PFS and OS of cancer patients and MPM.

Keywords: Mesothelioma, Prognostication, Hyponatremia

Introduction

Malignant pleural mesothelioma (MPM) remains an incurable and with very poor outcome cancer. The median survival of 12 months with first line therapy [1] and the median survival of 24 months at best when treated with multimodal approach (either neoadjuvant chemotherapy and surgery with or without radiation therapy or postoperative chemotherapy) [2] a staging system that is not ideal, considering the diffuse nature of the disease and its variable biology [3] difficulties with surgical resection, often resulting in R1 or R2 resections which even in specialist centres carry a prognosis of between 7-12 months alongside operative mortalities of 5%. There is a subpopulation of MPM patients with favorable biology and in these cases a multimodal approach with intense therapy may improve prognosis. Novel techniques and biomarkers are required to enhance our ability to identify this group of patients who may then benefit from more aggressive treatment strategies. Furthermore, the ability to accurately identify patients with poor prognosis tumours may enable true patient centered care to be offered in terms of palliative treatments or best supportive care. Ultimately prognostic markers are required not only purely to predict prognosis but also to enable us to assess response to therapy during treatment thus enabling us to identify patients who are not responding early and to explore further treatment options for these patients.

Finding a reliable prognostic factor in MPM would be extremely important. It has been previously explored by considering many variables, usually one at a time, at many centers, all with limited numbers of patients and often using retrospective data. The variables can be purely clinical, such as patient demographics, which are frequently combined with standard laboratory values including white cell count or platelet count. Other investigators have concentrated on

radiologic parameters at presentation as determined by scrutiny of computerized tomograms (CT) or positron emission tomography (PET) alone or fused with CT. Finally, a molecular pathologic approach, using state of the art platforms such as genomics, microRNA, epigenetics, or proteomics is used in order to define single or combinations of candidate prognostic biomarkers from tissue or blood.

The best-known clinical prognostic scoring systems for MPM have been developed by European Organization for Research and Treatment of Cancer (EORTC) and Cancer and Leukemia Group B (CALGB) [4] combination of biological and clinical factors.

Poor performance status, non-epithelioid histology, male gender, low hemoglobin, high platelet count, high white blood cell count, and high lactate dehydrogenase (LDH) were found to be poor prognostic indicators in mesothelioma. The EORTC model was validated at St. Bartholomew's Hospital in a group of 145 patients treated in sequential phase II chemotherapy trials.As a follow-up on the EORTC data, a prognostic index for progression free survival revealed that age, histological subtype, stage, performance status, hemoglobin and WBC levels were independent predictors of time to progression [5]. The prognostic significance of other demographic factors including adjuvant therapy, WBC, hemoglobin, smoking history, asbestos exposure history, performance status, chest pain, and weight loss are also being investigated.

Prognostic factors are biological or physical characteristics of a patient or a patient's cancer that can be used to predict an outcome for the individual. They may assist in the selection of patients most likely to benefit form more intensive treatment, especially in the context of clinical trials [6].

Among them hyponatremia has become increasingly interesting. It is the most common electrolyte disorder in hospitalized patients, hyponatremic cancer patients present with poor performance status, quality of life and prognosis of their Cancer [7]. Syndrome of inappropriate antidiuretic hormone syndrome (SIADH) is a frequent of Hyponatremia in cancer patients, due to ectopic production of antidiuretic hormone.

We therefore performed a retrospective single institute analysis to assess and possibly confirm the prognostic role of hyponatremia in MPM.

Materials and Methods

We searched the electronic database of new referrals to our department for patients with newly diagnosed MPM from January 2009 and December 2014 who had received chemotherapy as part of their treatment. MPM was confirmed by histology or cytology in all cases. In total 88 patients with MPM were identified.

We collected data on age, date of initial diagnosis, overall survival (OS), performance status (PS), serum sodium values and tumor response to first and if appropriate second line treatment according to RECIST criteria [8].

Hyponatremia was defined as serum sodium values below 135 mmol/l [9]. Severe Hyponatremia was present if sodium values were measured at or below 130 mmol/l.

First line chemotherapy was either with Cisplatin 75 mg/m^2 iv or Carboplatin AUC 5 and Pemetrexed 500 mg/m^2 Iv day one every 3 weeks in 88 MPM (100%). If patients progressed after first line chemotherapy and were considered fit they were offered second line chemotherapy with Vinorelbine orally 60 mg/m^2 day 1 and 8 or rechallenge platinum based chemotherapy if progression free survival greater than 12 months.

Response was evaluated with CT scans in all patients using RECIST criteria. OS was defined as the time between histological diagnosis and the last follow up visit or death, while PFS was calculated from the start of chemotherapy to the date of progressive disease or death.

The method of Kaplan and Meier [10] was used to calculate survival curves. To assess the statistical significance of difference between the survival curves we performed log-rank tests. The Cox multivariate proportional hazard regression model was used to evaluate the effects of the prognostic factors on PFS and OS.

Results

We identified 88 cases within our database, predominately male (75%) with median age 68 (range 52-78). Main clinical characteristics are listed. All patients received first line palliative chemotherapy with platinum (ether cisplatin or carboplatin) and Pemetrexed. 20 patients (23%) had partial response, 28 patients (32%) had stable disease had and 40 patients (45%) had progressive disease as best response to first line therapy. Second line chemotherapy with oral Vinorelbine or rechallenge platinum based chemotherapy if PFS > 12 months, was given in 43 patients.

The median OS was 11.8 months and the PFS was 4.5 months (range 0.7-18.5) after first line and 3.5 months (range 0.3-16.5) after second line. Twenty-one pts (24%) developed hyponatremia throughout the treatment; the OS for these patients was worse (8.1 months) compared to the patients with normal sodium serum level (OS 14.4 and $p<0.001$). No patients presented with hyponatremia before receiving chemotherapy. Patient with normal sodium serum level throughout the treatment had a PFS of 6.45 months whereas in the hyponatremia group the PFS was 3.2 ($p<0.004$).

Second line chemotherapy was given in 40 patients in the non-hyponatremia group but only 7 patients within the hyponatremia group received second line treatment. The PFS in this group was 1.4 months ($p<0.002$) compared 3.8 in the normal serum group.

Discussion

In this retrospective analysis of a single institution series of 88 MPM we found that hyponatremia was associated with poorer prognosis. The findings confirm what already reported in at least a similar, previous Italian study [8].

Hyponatremia is a very common electrolyte disorders in MPM with a potential role as a prognostic biomarker. Very little is known about hyponatremia in cancer patients although there have been a recent increased interest on this topic [9,11]. The main cause of Hyponatremia is SIADH which often caused by ectopic production of arginine vasopressin (AVP) and atrial natriuretic peptide (ANP) by the cancer [12]. Other causes of hyponatremia are diarrhea or vomiting causing hydration and narcotic drugs [13].

Hyponatremia in cancer patients has been reported as a poor prognostic factor in at least 3 different studies [14-16].

Several studies have identified prognostic factor in MPM [15,17] but none of them evaluated the role of hyponatremia. The two scoring systems, one form the EORTC and the other form the CALGB include

gender, age, performance status, histology and site of disease, as well as laboratory parameters such as hemoglobin, LDH levels, blood count of platelets and leucocytes.

Treatment options for patients with subnormal serum sodium levels are fluid restriction or sodium supplementation [18]. Tolvaptan, a selective oral vasopressin V2-receptor antagonist was assessed in patients with chronic heart failure and led to increased urine production and normalization of sodium value without needing to adhere to fluid restriction [16]. EMEA approved Tolvaptan for treatment of hyponatremia form SIADH in 2009 but the treatment costs are still high and might impede a more widespread use of this new approach.

If patients received treatment for hyponatraemia the majority of our patients received hypertonic saline infusion (65%), 35% were treated with demeclocyclin and fluid restriction.

The OS and the PFS in the hyponatremia group are inferior to the patients who had normal serum sodium level throughout the treatment. None of our patient presented with hyponatremia, but having sodium serum level <130 at some point during chemotherapy was a strong indicator of short PFS and a negative prognostic factor. The findings were similar in first and second line setting.

We are aware of the limitations of the study: the retrospective and single institution design are weaknesses as well the lack of information about the management of the hyponatremia in every case but on the other hand all sodium levels were obtained with the same laboratory equipment and among all the patients reviewed there had been with no drop out at follow up.

Conclusion

A common condition such as Hyponatremia in cancer patients could be a prognostic marker in MPM. Most of the studies have proved the low serum sodium to be a prognostic biomarker at baseline; our data suggests that this could be of value even throughout the treatment, first or second line.

Early detection and correction of the cause of hyponatremia could have an impact on the PFS and OS, careful consideration should be given to the new molecule Tolvaptan, V2 receptor antagonist, in the management of cancer induced SIADH and trials should be designed to address this question.

We are now planning to analyses our data together with a large series of MPM patients treated at the mesothelioma unit of Casale Monferrato and Alessandria Hospital, located in a heavily industrialized area in Piedmont, Italy where asbestos exposure is prevalent. If this further analysis confirmed our initial findings, further prospective trials would be certainly warranted to better explore the role of sodium correction on the PFS and OS of MPM on while on anticancer treatment.

References

1. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, et al. (2003) Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21: 2636-2644.
2. van Meerbeeck JP, Scherpereel A, Surmont VF, Baas P (2011) Malignant pleural mesothelioma: the standard of care and challenges for future management. Crit Rev Oncol Hematol 78: 92-111.
3. Rusch VW (1995) A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group. Chest 108: 1122-1128.
4. Edwards JG, Abrams KR, Leverment JN, Spyt TJ, Waller DA, et al. (2000) Prognostic factors for malignant mesothelioma in 142 patients: validation of CALGB and EORTC prognostic scoring systems. Thorax 55: 731-735.
5. Francart J, Vaes E, Henrard S, Legrand C, Baas P, et al. (2009) A prognostic index for progression-free survival in malignant mesothelioma with application to the design of phase II trials: a combined analysis of 10 EORTC trials. Eur J Cancer 45: 2304-2311.
6. Steele JP, Rudd RM (2000) Malignant mesothelioma: predictors of prognosis and clinical trials. Thorax 55: 725-726.
7. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G (2006) Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med 119: 71.
8. Byrne MJ, Nowak AK (2004) Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Oncol 15: 257-260.
9. Turrisi AT 3rd, Kim K, Blum R, Sause WT, Livingston RB, et al. (1999) Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 340: 265-271.
10. Kaplan EL, Meier P (1958) Non parametric estimation form incomplete observations. Am Stat Assoc J 457-481.
11. Hermes A, Waschki B, Reck M (2012) Hyponatremia as prognostic factor in small cell lung cancer--a retrospective single institution analysis. Respir Med 106: 900-904.
12. Sørensen JB, Andersen MK, Hansen HH (1995) Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. J Intern Med 238: 97-110.
13. Bissett D, Cornford EJ, Sokal M (1989) Hyponatraemia following cisplatin chemotherapy. Acta Oncol 28: 823.
14. Bergmans T, Paesmans M, Body JJ (1999) A prospective study on hyponatremia in medical cancer patients: epidemiology, etiology and differential diagnosis. Support Care Cancer 8: 192-197.
15. Doshi SM, Shah P, Lei X, Lahoti A, Salahudeen AK (2012) Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. Am J Kidney Dis 59: 222-228.
16. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, et al. (2006) Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 355: 2099-2112
17. Curran D, Sahmoud T, Therasse P, van Meerbeeck J, Postmus PE, et al. (1998) Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. J Clin Oncol 16: 145-152.
18. Herold G (2006) Internal Medicine. A lecture-oriented presentation. Considering the subject catalog for medical examination. With ICD-key pp: 691-691.