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Fellowship topic:

Development of a new protocol for the treatment of bowel obstruction

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Introduction:

Malignant bowel obstruction affects more than 10% of patients with advanced cancer, and is associated with a decrease in life expectancy (less than 90 days of median survival even in selected patients), and high healthcare associated costs derived from the complexity of managing this complication in an outpatient basis.

Regardless of its high frequency there is a lack of well designed, well powered and consistent clinical trials evaluating the best treatment options for malignant bowel obstruction, and our current treatment practices are based in small unicentric studies, that are very sensitive to differences in prognosis in the experimental and control groups.

Another problem is the heterogeneity in the definition of success in the treatment of malignant bowel obstruction, and the fact that objective measures such as overall survival and length of hospitalization do not measure the true objective of the treatment: to achieve symptom control. Many investigators have proposed different endpoints such as the presence and severity of obstruction-associated symptoms and use definitions for “resolution” of bowel obstruction, that differ in the length of the symptom free period before declaring a patient “free of obstruction” or if any residual symptomatology is allowed.

Since bowel distension, pain and vomiting are most frequent symptoms different symptomatic treatment strategies that combine analgesics, antiemetics and inhibitors of bowel secretion have been used in the past, but the benefit of newer drugs versus older drugs that seek the same role such as somatostatin analogues versus anticholinergics or serotonin inhibitor versus anithistaminics or neuroleptics has not been established with a high quality level of evidence.

Other controversial aspects of malignant bowel obstruction is the role of corticoids in the management of the disease with some small studies that report a benefit in symptom control in some cases, the role of venting gastrostomies to reduce vomiting and the selection of cases that are candidates for more aggressive treatment.

In any case since the mortality and morbidity of surgery in malignant bowel obstruction is high and the long term results are poor, it is important to evaluate the patient long term goals and conduct an adequate decision-making process that involves the patients and their families.

One problem is that are no validated instruments to measure prognosis specifically for bowel obstruction that often occurs as an acute event before the patient has initiated end-of-life planning or suffered from significant deterioration.

This project ties to lay the basis of a new era in the treatment of malignant bowel obstruction, delimiting the prognosis for each patient based in the specific risk factors, so patients and doctors have a better understanding of their prognosis and researches will have a better idea of in which patients a clinical trial to determine the better treatment for bowel obstruction should be conducted.

Goals of the Project:

1 Review the practices of treatment of malignant bowel obstruction in different settings

2 Elaborate a systematic review of the published literature on bowel obstruction to identify the best current evidence and prognostic factors in bowel obstruction

3 Propose a new protocol of management for bowel obstruction

4 Validate a new prognostic score based used clinical criteria that stratifies good vs bad risk cases at admission

Results:

We managed to identify differences in practice between the home and host institute**,** not only on the pharmacologic treatment that was initiated but also in the likelihood of using interventional and surgical approaches.

A brief review of 115 patients recorded in two years in the home institution is resumed in this table.

		N =115	%
Sex	Male	49	42
	Female	66	57
Histology	Gyn	23	20
	Bowel	40	34
	Biliopancreatic	14	12
	Gastric and GEJ	17	14
	Other	21	18
Obstruction		14	12
Peritoneal disease		47	41
Stage IV		49	43
Surgery		79	69
Abdominal radiation		27	24
Stent		3	<3
Chemotherapy		100	86

At admission patients had in their majority known stage IV disease (75%) with previous evidence of peritoneal carcinomatosis in 63% of cases and of intra-abdominal infiltrating masses in 49%, but only half of the patients were receiving active chemotherapy. Nearly all patients presented symptoms like pain (98%) and nausea (91%), followed by vomit and abdominal distension and a deterioration of their performance score (9% PS0-1, 43% PS2, 33% PS3, 13% PS4). Palliative prognostic index (PPI) altered items were mainly oral intake (64%) and edema (21%). They were treated with anti-secretors (octreotide 58%, butyl scopolamine 26%), anti-emetics, (ondansetron 65%,

metoclopramide 46%) neuroleptics (60%), corticosteroids (59%) and analgesics (opioids in 66%). The episode of obstruction could be resolved in a median of 12 days in more than half of our patients (59%), this led to an acceptable rate of outpatient management of 61%, nerveless the prognosis of these patients was still very poor, with a median survival from the moment of obstruction of only 42 days and a rate of re-obstruction of 52%.

A systematic review was performed using the terms “malignant bowel obstruction” “peritoneal metastases” and “inoperable bowel obstruction” in pubmed, SCOPUS, the Cochrane database proceedings of oncology, surgical oncology and palliative care meetings and google scholar.

206 reports were selected for review, published between 2000 and 2012, after excluding case reports, reviews, and surgical and interventional reports we found 8 studies with different methodologies assessing medical treatments in bowel obstruction; 3 prospective open label trials evaluating subcutaneous octreotide versus other anti-secretors, another two studies exploring the role of long acting somatostatin analogues in blinded randomized prospective trials, one retrospective series evaluating the use of olanzapine as antiemetic and one prospective, non-randomized study with a protocol that included dexamethasone, octreotide, metoclopramide and amidotrizoate.

The heterogeneity between these studies and the low number of patients included in them as well as the presence of different inclusion criteria precluded the realization of further analysis, but they supported the recommendations of the available guidelines that recommend to initiate medical treatment before the pathological feedback between bowel distension and increase in bowel secretions has started and the use of at least an anti-secretor (with a preference of octreotide) and an antiemetic in combination with a trial of corticosteroids, as well as localizing the point of obstruction using diagnostic imaging for consideration of interventional techniques.

We were also able to identify 3 large series and 5 systematic reviews that proposed several prognostic factors such as the performance score, the use of surgical of interventional techniques, the level of albumin and the origin of the primary as prognostic factors.

Since it is important to determine the best treatment strategy as soon as possible we evaluated a multivariate model including only factors that are part of the medical history, items that are easy to evaluate by physical examination or symptoms that can be assessed at admission and routine laboratory parameters.

We correlated the presence of this factors with a primary outcome, symptom resolution, defined as the presence of controlled pain (EVA<3), 1 or less episodes of nausea-vomiting, and the presence of adequate oral intake for at least 48 hours and four other outcomes; overall survival, readmission free survival, length of hospitalization and the ability to be managed in an outpatient setting.

Four clinical variables were statistically associated with survival (p< 0,005 multivariate Cox regression): presence of ascites, delirium and low conscience level, a non-gynaecological-non intestinal primary, and known metastatic

disease at admission. Three variables were correlated with resolution of symptoms (p< 0,05 Chi Square): a PS score of less than 3, absence of progressive disease, and a non-gynaecological-non intestinal primary.

We generated a 4 item prognostic index analysing 115 consecutive cancer patients treated at our institution from 2008-2010 for a first episode of bowel obstruction. We analysed the influence of treatment for four principal outcomes in the high and low risk population, as established by the score. Using this variables we generated a 4 item score with an AUC of 0.751. Using a threshold of 2 risk factors permitted us to categorize 51,7% and 45,6% of the patients respectively as low risk patients.

The four item score allowed us to predict the resolution of symptoms with sensitivity of 74,5 and a specificity of 73%, and the possibility of discharge with a sensitivity of 76% and a specificity of 68%. The median overall survival in patients with a low risk score was 14 weeks versus 2 weeks for high risk(p< 0,01 log rank test) and the median length of hospitalization was 15 vs 52 days (p< 005 log rank test).

Description of the time spent in the Host Institute:

The time spent I spent in the Hospital da Luz has completely changed the way I interact with my patients and even my image of our role as doctors.

Dr Neto is a strong advocate of the dignity conserving care model in palliative care and speaking with her but also having the opportunity to see how the medical and nursing team at the Unidade cooperated to seek the wellbeing of their patients using mainly their interaction with them has made me realize the therapeutic potential of the doctor-patient relationship like nothing else before.

A typical day in the unit while I was there would start with Dr Neto and me reviewing the comments of the nursing team and the new patients that where admitted at any time of the day, and preparing a comprehensive evaluation of what where the needs and objectives for each patient, and it would continue by meticulously planning the rounds and the family conferences with the nurses (all of them with specialized training in palliative care).

There was no fixed timeslot for rounds, the time allocated to each patient interact would depend on the patient preferences and trying to maximize their comfort, but we would usually see new patients and patients with more difficult issues first. Up to 50% of the patients at any time were cancer patients, but dementia and other neurological problem were well represented and we could also see patients in rehabilitation or long term care occasionally.

During these visits we not only evaluated the physical health of our patients, we also used different dignity-conserving affirmations and careful questioning to discover if additional therapeutic interventions to bolster patient autonomy and dignity were also needed.

The treatments were revised at least daily and as many times as necessary if the symptom control was poor and the higher degree of shared decision making was used whenever possible to preserve patient dignity and promote social dignity.

Family conferences were usually scheduled with days in advance and later in the day so adequate time could be allocated for them and a coherent objectives for each meeting could be proposed. I was sincerely amazed by the profundity and sincerity of this conferences and the ability of the medical team to discover the causes of behaviors and misunderstanding that I was not even aware that existed and their ability to manage concerns with a balance between delicacy and sincerity.

Whenever was appropriate the admitting specialists, specially the oncologists were encouraged to visit the patients and take part in discussions about their care and I felt during my stay that even my vision as a medical oncology fellow was respected and valued.

I had the opportunity to discuss my project with Dr Neto before, during and after the fellowship period, including a presentation of the preliminary descriptive analysis in presence of all the palliative care team, and her comments and suggestions were invaluable in the analysis and elaboration of a score that intends to be useful not only to specialist but to emergency and primary care physicians.

I also learned a multitude of “tricks of the trade” from her ample experience in palliative care and was delighted in her recommendations of new literary and philosophic texts that have helped me understand better the end-of-life experience.

Due to high similarity between Galician and Portuguese I was able to interact with patients and staff with little difficulty and during the last weeks of my stay I had the opportunity of trying to implement my new communication abilities with some patients that consented to be interviewed by me.

I want to acknowledge here the role of Dr Neto and the rest of her team in helping me through some especially difficult conversations and give her my gratitude for her support and mentorship.

I would also like to take this opportunity of thanking the European Society for Medical Oncology (ESMO) for granting me this opportunity and Weleda as the sponsors of the ESMO Palliative Care Fellowship.