

SINPE Position Paper on the use of home parenteral nutrition in cancer patients

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Although the first report of Home Parenteral Nutrition (HPN) in cancer patients dates back to 1975 [1], its use has never gained wide acceptance among oncologists. Only in recent years, HPN has prompted renewed interest [2–4] possibly because the availability of new anticancer drugs made imperative to allow completion of scheduled therapies to achieve full benefit despite treatment-associated toxicities.

A major barrier to develop and implement programmes of HPN in cancer patients is the lack of statistically robust randomized controlled trials (RCTs) on which informing strong recommendations in international guidelines. However, it

has been already noted [5] that the peculiar design of nutrition trials may not fully fit the procedures required to issue guidelines. In particular, the inclusion of a no-nutrition arm may not be ethically possible when hypo- or aphagic cancer patients are studied.

Furthermore, the growing awareness of the role of inflammation in the pathophysiology of cancer cachexia has led some oncologists to underestimate the potential of the nutritional support as if the hypophagic cachectic patient ceased to require nutritive substrates to sustain the body physiologic functions.

Finally, the uncertainty about the indications of HPN is also due to the marked heterogeneity of patients in the series reported in literature and the consequent inevitable controversial results.

Since the major outcome determinants of cancer patients potentially candidate for HPN are the curability of the tumour (which depends on primary's type and stage), the nutritional and the performance status, and the severity of the hypophagia, it should be important for the studies investigating the effect of HPN in this patients' population to account for these variables. Alternatively, even well-made systematic reviews and meta-analyses on this topic [6, 7] are destined to remain little conclusive.

In the attempt to overcome this stalemate, a board of experts of the Italian Society for Nutrition and Metabolism (SINPE) has drawn a position paper with the aim of assessing the indications for HPN in cancer patients as a function of the above-mentioned clinical conditions, an approach originally devised in the SINPE guidelines on Artificial Nutrition in the Hospitalised Patient in 2002 [8]. This paper is not intended to go through the practical and the logistic aspects of HPN and concerning these issues we endorse the recommendations recently published by ESPEN [9].

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Moreover, this paper is not intended to discuss the option of the oral/enteral versus the parenteral approach, a decision which relies on the clinical judgement of the physician and the informed consent of the patient. Rather, it emphasizes the tenet that it is not possible any evaluation of the potential of the PN in the cancer patient if such treatment is not contextualised in the main clinical directives which are, depending on the different situations, to substitute a failing intestinal function, to potentiate the oncologic therapy and to prolong survival and/or quality of life (QoL) in starving severely malnourished patients.

Before going through the core of the issue it is important to point out that, as a general rule, a cancer patient potentially candidate for parenteral nutrition (PN) could enter a programme of HPN if two main requirements are met: 1) the same programme of care provided in hospital can be safely replicated at home and, 2) more relevant, the patient's desire to go home and logistic conditions allow this. Both these two conditions are somewhat binding.

There are two potential advantages of HPN comparing with in-hospital PN.

- a) Providing PN in a home-based setting is expected to reduce hospital costs [10] which range from 83€, to 25–124€, to 74–121€ per day in France, Spain, UK, respectively [11–15]. Different organisation of HPN programmes from one centre or country to another, which influences the choice of the elements included in HPN expenditure, can account for differences in costs estimation. According to a recent Italian report [16] the daily cost of the solution, infusion line and dressing kits was 36.34€ for HPN.
- b) For the patients too, there should be a reasonable expectation of achieving a better QoL if they prefer to receive PN at home rather than remaining in hospital.

There are 3 main potential areas for the use of HPN in cancer patients:

Class 1: patients with minimal/null tumour burden but with chronic intestinal failure [17], Class 2: patients undergoing an intensive anticancer therapy with severe gastrointestinal toxicity or chronic insufficient food intake. These patients might not necessarily be in a poor nutritional status when they start the oncologic treatment and PN is often administered as a supplemental nutrition (SHPN), and Class 3: incurable (hypo)-aphagic malnourished patients.

Literature does not always discriminate among these classes and this may make difficult to interpret the results of HPN in different publications. Furthermore, a migration from class 2 to class 3 is possible for some patients originally receiving SHPN during an anticancer therapy which finally proves unsuccessful, while the patient still complains

of a very poor nutrient intake and hence requires nutritional support.

Class 1 includes a small subset of patients characterised by chronic intestinal failure [17] and with a minimal or null tumour burden. The intestinal failure in these cases is generally caused by mechanical obstruction or short bowel syndrome due to surgical or radiation therapy complications. The outcome of these patients depends on the progressive nutritional deterioration (if not adequately treated) rather than on recurrence or progression of the tumour and hence they should benefit from receiving HPN. Some of these patients may be finally weaned from HPN because of the spontaneous resolution or medical/surgical treatment of their intestinal failure. *Class 1 patients should be treated according to the existing guidelines of HPN for the chronic intestinal failure* [18].

Class 2 includes a growing segment of the cancer patients on oncologic therapy and receiving HPN (usually a SHPN) because gastrointestinal toxicity or malnutrition (pre-existing or occurring during an intensive oncologic therapy) might reduce the compliance with the treatment. This would lead to a delay or a dose reduction of the further cycles of anticancer therapy which could finally result in a less effective cure.

It is reasonable to expect a benefit of this SHPN in two conditions: the nutritional conditions of the patients are so compromised or gastrointestinal toxicity so severe to adversely affect the planned administration of the oncologic therapy, and the oncologic therapy is so effective to translate into a clinical benefit. A secondary end-point of SHPN is the attempt to improve or preserve the QoL of the patients relying on the hypothesis that improving the nutritional status can lead to a better QoL [19].

To date, 3 RCT [20–22] have analysed the effect of SHPN on different outcomes: one [20] reported that there was no difference between SHPN patients and controls as regards body composition and working capacity but SHPN patients were able to receive a higher dose of chemotherapy. Both the remaining studies [21, 22] reported no difference in survival between SHPN patients and controls. However it should be pointed out that, for ethical reasons, the nutritional status of the enrolled patients was not so compromised to interfere with the schedule of chemotherapy and the anticancer treatment was given with a palliative rather than a curative intent. This means that, at the present time, in front of the question “does SHPN improve the outcome of malnourished cancer patients on intensive anticancer therapy” we face an absence of evidence, rather than an evidence of an absence of effect [23].

The effects of SHPN on QoL were investigated in 6 prospective studies using validated questionnaires on QoL (but without a control group) [24–30] and overall they showed a benefit in some domains of QoL. These findings are

penalised because these studies lacked a control group and it was not possible to define the relationship between change of QoL and response to the chemotherapy. Of the two RCT one [21] showed a benefit in QoL at 3 months, the second [22] no benefit. However the two studies are not strictly comparable also because the median survival was 5.6 months in the first [22] and only 2.6 months in the second one [23]. This interval time might be too short to achieve a benefit since a previous prospective investigation on QoL of incurable cancer patients on HPN has shown that QoL tends to deteriorate in the last 2–3 months of survival [31].

Altogether the data show that a benefit in QoL is possible with SHPN even if it is clear that herewith we are in the grey area of the “suggestion” rather than that of the “recommendation”. However *certainly the potential of SHPN in malnourished cancer patients on intensive anticancer therapy is worthy of being considered in the clinical practice.*

Since an argument against the usage of SHPN is the risk of catheter related bloodstream infection (CRBSI), it should be considered that SHPN patients maintain even some amounts of oral intake and this strategy may reduce the cholestasis and prevent the CRBSI [32, 33]. In this regards it is also interesting to note that the risk of CRBSI in adult HPN patients ranges within 0.35–1.74 per 1000 catheter-days [34–40], and the lowest rate of 0.29 per 1000 catheter-days was reported in a sample of 761 HPN cancer patients [41]. Furthermore, the PN-associated liver disease is unlikely to occur if the prognosis is less than 18 months, a duration of HPN almost never reached in this patients’ population.

Class 3 includes a very selected subset of malnourished hypophagic incurable patients who are expected to die prior from nutritional deterioration than from tumour progression. The most frequent reasons for aphagia are the severe anorexia as a component of a cachectic syndrome or the presence of a malignant chronic small bowel obstruction. Most

of these patients have exhausted all the available anticancer therapies but a few can actually still receive some anticancer treatment just for some palliative intent. Some of them reach a regimen of total HPN after having received for some weeks/months only a supplemental nutritional integration. This is the group in which the indications are more controversial and an appropriate answer cannot disregard that the outcome of these patients, potentially candidate for HPN, is conditioned by several determinants beyond their condition of starvation.

The most compelling point is the estimation of the life expectancy because, as a matter of principle, a programme of HPN can be successful in prolonging the survival only if the patient is expected to die prior from starvation/malnutrition than from tumour progression. Since a vast literature has shown that without nutritional support a severely malnourished (hypo)aphagic cancer patient can survive only few weeks (see ref. in 42), there is a rationale for using HPN only if the survival due to the tumoral spread is expected to be longer than a couple of months, a statement already supported by the European Association for Palliative Care 25 years ago [42].

Class 3 includes a vast heterogeneous patients population characterised by different prognostic indicators as type of primary (some slow-growing unresectable retroperitoneal tumors, ovarian and neuroendocrine cancer having more favourable outcome [7, 43–46]), tumour spread, Karnofsky performance status [47–52], severity of weight loss or cachectic status [15], low albumin level [53], Glasgow Prognostic Score [44]. Following a multivariate analysis of some prognostic factors (Karnofsky Performance Status, Glasgow Prognostic Score, tumour spread, site of primary: gastrointestinal, ovary, other) in a series of several hundred patients included in a prospective multi-institutional study on HPN [44], a nomogram was built which allows an

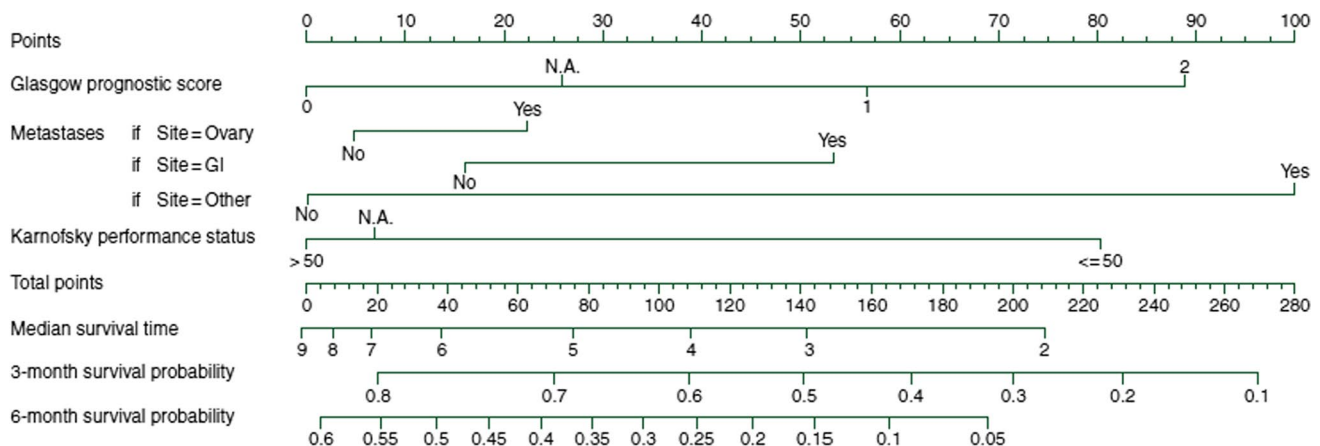


Fig. 1 Cox modeling based nomogram for predicting 3-, 6-month and median OS. Instructions on how to use the nomogram for building survival estimates are supplied at the bottom of the Results section

approximate estimate of the length of survival of these incurable cachectic patients (Fig. 1). This ranges from less than 1 month to more than 9 months and can help the clinician to modulate the strength of the recommendation in favour of or against the HPN. Survival of these patients is generally much shorter than that of patients receiving SHPN and chemotherapy [54].

Since the literature shows a broad variety of results, we would only focus on a few extreme reports. Lundholm et al. in a RCT [53] comparing HPN patients (total calorie load 34–35 kcal/Kg/d) with controls receiving 23–24 kcal/Kg/d reported that, by an as-treated analysis, intravenously supported patients had a significantly longer median survival than no-HPN patients (about 11 versus 7 months, respectively). On the other hand, if we consider patients with several negative prognostic factors, survival with HPN may be only very few weeks. It is intriguing, however, the recent observation of a quasi-RCT [55] showing that also in the prognostically poorest subgroups of patients, HPN was able to achieve an almost three times longer survival comparing with no-HPN controls.

A very hot issue is the potential effect of HPN on QoL. The findings of the literature showing that the grade of weight loss [56] or of the BMI-adjusted weight loss [57] are correlated with QoL in advanced cancer patients do not mean that the improvement of the fat-free mass, which is possible through PN [21, 58–60], translates in a better QoL. QoL is a multidimensional construct and cannot be reduced to the nutritional status only. The few data of literature [28, 31, 61] would show that a transient improvement in some domains of QoL is at a very least possible and a recent paper [62] reported that there was no difference in Parenteral Nutrition Impact Questionnaire scores between people with an underlying diagnosis of cancer and those with other underlying disease states such as inflammatory bowel disease.

QoL is an individual experience and this underlines the need of refraining from modulating the indication for a HPN on the basis of literature data and emphasizes the opportunity of evaluating patient by patient.

Patients and their families prefer clear and honest information rather than a lack of information [63] and both have to be aware of the potential advantages and disadvantages of HPN and of the agreed targets that, if not attained, will dictate the option to withdraw HPN. The clinicians, on the other hand, can propose but cannot force the option of a HPN programme in the favourable cases, and, in the same way, they should be very cautious to deny it if a poor candidate request it.

In conclusion, we suggest that in order to achieve survival and QoL benefits by HPN, *patients with cancer should deserve an individualised evaluation, weighing up both the objective prognostic factors and the personal*

patient's preferences before starting a programme of HPN and, in very uncertain situations, a trial and error approach might be proposed.

Declarations

Disclosure FB reports speakers' honoraria from Baxter.

RC has served as scientific lecturer and/or consultant and/or on advisory panels for Baxter, Fresenius Kabi and BBraun.

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LP declares no conflict of interest.

LS declares no conflict of interest.

MZ declares no conflict of interest.

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