

Neurokinin A is a sensitive prognostic indicator for neuroendocrine tumours of the midgut and is useful to the clinician when considering treatment options

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Introduction

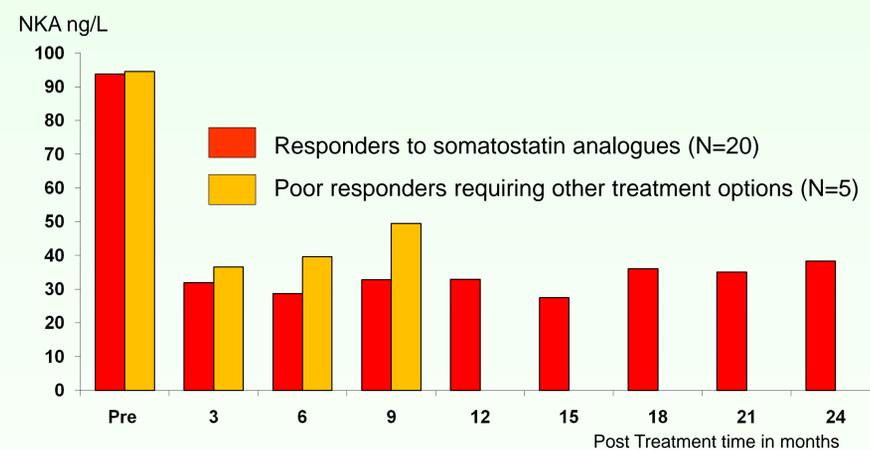
Endocrine tumours of the midgut (MGC) are one of the most common neuroendocrine tumours with an incidence of about 1:100,000 per year. They may present early with acute small bowel obstruction or later with carcinoid syndrome or with the signs of metastatic disease. Even when hepatic metastases are present disease progression is very variable. Some tumours remain indolent for many years, while others are aggressive and difficult to manage. Assessing prognosis is therefore important so that tumours that will be aggressive are treated immediately and appropriately while patients with those that are indolent may not be subjected to unnecessary therapies.

Clinicians traditionally use radiography to identify secondary disease and to monitor for recurrence post treatment. Scans are, of course, expensive and may use radiation therefore frequent testing and retesting is not an easy option. It has recently been noted that Chromogranin A (CgA) rises after radical surgery, indicating recurrence of disease, significantly earlier than any change observed using state of the art radiology (Stridsberg et al 2009).

In 2006 we published the findings of a retrospective study in a group of patients with MGC followed over a fifteen year period. We found that raised circulating neurokinin A (NKA) was a more sensitive marker of disease than CgA or indeed Urinary 5 HIAA. Raised NKA was also shown to be an independent indicator of poor prognosis. The most exciting finding was that the most recent NKA gave the most accurate prognosis, suggesting that lowering NKA could possibly improve prognosis.

We can illustrate that standard treatments, used for these tumours, lowers circulating NKA. Figure 1 shows NKA response to long acting somatostatin analogues over a 24 month treatment period in 25 patients. Twenty of the 25 patients showed a sustained response to treatment over 15 months with a very gradual rise in NKA thereafter, whereas 5 of the group showed only a transient response and further therapeutic intervention was necessary and was commenced in this sub-group at that stage.

Figure 1



Study

The Royal Victoria Hospital in Belfast has a tertiary referral clinic for NETs. Since 2002 in the NET clinic we have used circulating NKA results when assessing patients with MGC. When treating we address symptoms, disease stage as assessed by histology, disease burden as assessed by radiology and prognosis as assessed by circulating NKA.

In a laboratory audit of NKA tests carried out for patients in Northern Ireland all NKA results that were >50ng/l (RR 20ng/l) between 1 January 2002-31 December 2010 were compiled. Patient records were examined and the following data were collected

- 1 Histological diagnosis of tumour type
- 2 Attendance at the NET clinic
- 3 Treatment
- 4 All subsequent NKA results from those patients
- 5 Survival outcome

Only those patients that had the diagnosis of neuroendocrine tumour of the midgut, confirmed by histology and only those that survived more than 2 months from the initial NKA test were included.

Results

There were 97 individual subjects from Northern Ireland whose NKA was, or rose >50ng/l during the test period. No diagnosis was secured in 2 and survival was less than 2 months in 10. Eighty five patients were included for analysis.

Figure 2 shows the comparison of survival outcome from the date when NKA first rose >50ng/l between patients whose NKA was not reduced below 50ng/l thereafter and those whose NKA was reduced for 6 months or longer. Survival was significantly improved in the group whose NKA was reduced ($p < 0.0001$). Red bars show censored patients.

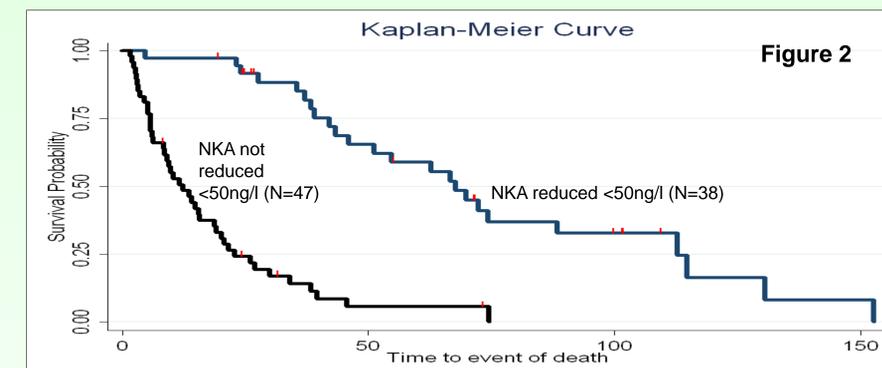
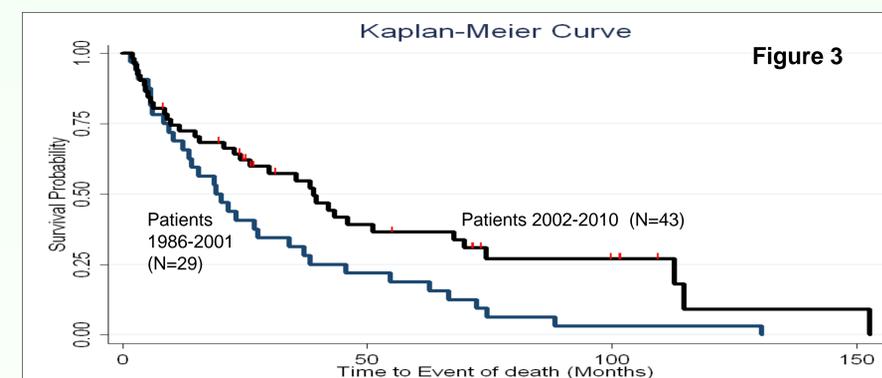


Figure 3 shows a comparison of survival outcome from the date when NKA first rose >50ng/l for patients presenting 1986-2001 and those presenting 2002-2010. The later group showed a significantly longer survival ($p = 0.0142$). Red bars show censored patients.

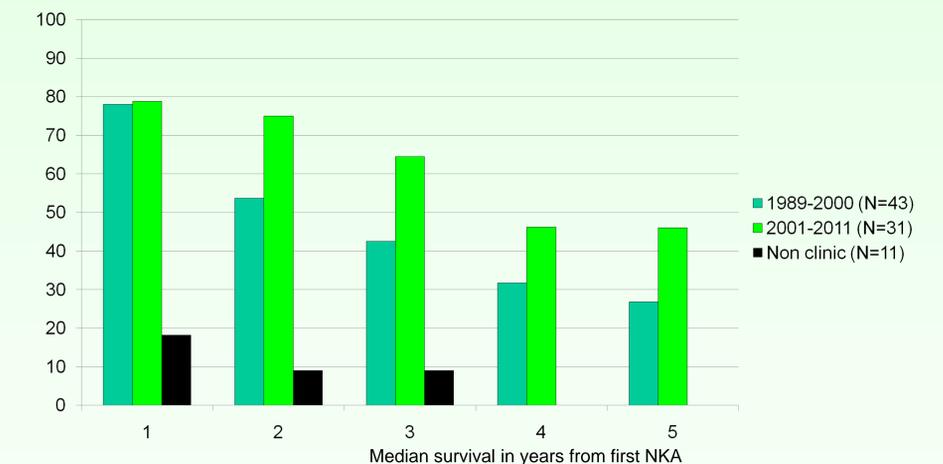


In an increasing number of patients, in the period 2002-2010, it has been possible to lower NKA below 50ng/l when the patient has presented with NKA above that threshold. This is no doubt due to the increasing range of treatment options available. The table below shows the comparison of data from the earlier and later time periods.

	1986-2001	2002-2010
Number presenting NKA >50ng/l	29	43
Number NKA reduced <50ng/L	7	26
Those reduced <50ng/L	24%	61%

Since the abstract was written survival data has been updated to 30 June 2012, which includes one further year. Figure 4 shows the 1,2,3,4 and 5 year percentage median survivals for patients 1986-2001, 2002-2010 and for patients who were not referred to the NET clinic. Survival in the later time period continues to improve as the patients in this group continue to survive. Although numbers are small patients not referred to a specialist unit have a poor outcome.

Figure 4



Conclusions

- 1 NKA, when raised >50ng/l is a sensitive prognostic indicator for poor survival in MGC.
- 2 When NKA is lowered through treatment, survival outcome can be improved.
- 3 In patient presenting with NKA >50ng/l lowering NKA should be actively sought.
- 4 By following these guidelines, survival outcome has improved in Belfast.
- 5 Patients attending a specialist unit for treatment can expect a better outcome.