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Commentary

ARCHIVES OF CLINICAL AND MEDICAL CASE REPORTS

ISSN: 2575-9655

Watch and Wait Strategies in NET Patients: More than Expected

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Keywords: NET; Survey; Watch-and-wait; Germany

Commentary

Neuroendocrine tumors of the gastroenteropancreatic (GEP-NET) system include sporadic and hereditary diseases which have been increasing in incidence recently [1]. In patients with resectable low grade well-differentiated neuroendocrine tumors (NET) surgery is the mainstay of therapy. However, the majority of patients present with unresectable disease, most frequently with liver metastases. In patients with low grade NET G1 (Ki67<2%) a watch-and-wait (W&W) strategy can be recommended in patients with loco-regional lymph node metastases or in patients with liver metastases if the liver tumor burden is low. The current German and European guidelines consider the use of W&W as a safe approach in this patient population [2, 3]. However, absence of symptoms and radiological tumor progression are essential requirements, along with a well-differentiated morphology and low grade as well as limited metastasis. The clearest evidence for an W&W approach in GEP-NET derives from the CLARINET trial, where a median progression-free survival (mPFS) of 18 months was achieved in the placebo group with tumor stability within 3-6 months prior to start of lanreotide [4]. Out of 103 patients in the placebo arm 60 patients experienced progression within 24 months. However, 43 patients demonstrated stable disease even after 2 years which confirms that a subgroup of patients has no need for therapy even in the long-term. Data on the current prevalence of patients with a W&W strategy are not available. In 2021, we surveyed NET patients in Germany, Austria and Switzerland to assess the medical care under the COVID-19 pandemic. The online survey (constructed by LimeSurvey software) was distributed via personal contact and by the patient organization NETZwerk NET e.V. In this process, 542 out of 684 NET patients completely answered all questions [5]. Of these, 68 (12.5%) patients indicated that they were followed by a W&W strategy. About half were between 41-60 years of age (n=36, 53.0%), 30 affected people were between 61-80 years (n=30, 44.1%). Most participants had a small bowel or pancreatic primary tumor with 25.0% (n=17) and 23.5% (n=16), respectively. 25% of the W&W group (n=17) self-reported a functional-active disease and 66.2% (n=45) displayed symptoms at the time of the survey. In most cases, the diagnosis required more than 12 months (n=30, 44.1%) and almost half of the participants have been living with the disease for more than 5 years (n=33, 48.5%). Present comorbidities were specified as follows: hypertension (44.5%, n=30), diabetes (19.1%, n=13), asthma/COPD (16.2%, n=11), chronic renal failure (13.2%, n=9), heart insufficiency (8.8%, n=6). Only one participant mentioned a chronic infection. Liver cirrhosis as comorbidity was not reported. All clinically available characteristics of the participants are listed in Table 1.

Our analysis demonstrates that the W&W strategy is frequently realized. However, there are no structured data on this approach in German or European NET registries or other databases [6, 7]. In general, a less frequent use of the W&W strategy was assumed, as therapeutic options have constantly evolved over the last 10 years. In earlier randomized phase III trials such as PROMID or CLARINET somatostatin analogues (SSA) were compared with placebo therapy. A similar approach was chosen for the RADIANT-3 and -4 studies, although here everolimus

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Citation: Sebastian Krug, Anja Rinke, Marianne Pavel. Watch and Wait Strategies in NET Patients: More than Expected. Archives of Clinical and Medical Case Reports 6 (2022): 534-536.

Received: June 23, 2022
Accepted: July 04, 2022
Published: July 21, 2022

Krug S et al., Arch Clin Med Case Rep 2022
DOI:10.26502/acmcr.96550511

Table 1: Clinical characteristics of 'watch and wait' participants.

n=542	Therapy n=369	(%) 68.1	Surveillance n=173	(%) 31.9	W&W n=68	(%) 12.5	All	(%)
Age								
18-40	14	3.8	8	4.6	2	2.9	22	4.1
41-60	169	45.8	85	49.1	36	53	254	46.9
61-80 and >80	186	50.4	80	46.3	30	44.1	266	49
Tumor localization								
small bowel	148	40.1	60	34.7	17	25	212	39.1
pancreas	85	23	46	26.6	16	23.5	134	24.7
duodenal	36	9.8	14	8.1	7	10.3	50	9.2
lung	23	6.2	15	8.7	4	5.9	41	7.6
CUP	30	8.1	9	5.2	6	8.8	42	7.8
others	47	12.4	29	16.6	18	26.5	66	12.2
Functional active								
yes	159	43.1	58	33.5	17	25	217	40
no (+ unknown)	210	56.9	115	66.5	51	75	325	60
Symptoms								
yes	269	72.9	104	60.1	45	66.2	373	68.8
no	100	27.1	69	39.9	23	33.8	169	31.2
Period from symptoms to diagnosis								
<3 months	79	21.4	48	27.8	19	27.9	127	23.4
3-12 months	79	21.4	44	25.4	4	5.9	123	22.7
>12 months	147	39.8	48	27.8	30	44.1	195	36
Therapy								
SSA	201	54.5					201	54.5
PRRT	29	7.9					29	7.9
CTx	29	7.9					29	7.9
TKI	15	4.1					16	4.3
W&W	68	18.4					68	18.4
Treatment setting								
ENETS center	122	33.1	56	32.4	21	30.9	178	32.8
University Hospital (none ENETS)	136	36.9	71	41	20	29.4	207	38.2
Non-university Hospital	49	13.3	15	8.7	10	14.7	64	11.8
Specialist practice	62	16.7	31	17.9	17	25	93	17.2

Duration of disease: 6, 8.8%, 29, 42.6%; 33, 48.5% (<12m, 12m-5y, >5y)

was investigated against placebo therapy [4, 8-10]. Except in the CLARINET trial, median PFS in the placebo arm was very low (6 months or less). However, the included patient populations were very heterogeneous, particular concerning tumor biology and disease manifestation, partly already pre-treated and therefore not comparable. Therefore, in the current ongoing trials different established treatment options are being evaluated. Especially since somatostatin analogues (SSA) are considered to have few side effects and to be safe, SSA are often used immediately after diagnosis. As already mentioned, a W&W procedure is appropriate in patients with defined criteria of a slowly growing disease, preferentially after initial diagnosis. But how can we assess tumor biology and tumor growth accurately after diagnosis? Post-hoc analyses of the CLARINET trial investigated the tumor growth rate (TGR), as independent marker associated with the progression-free survival (PFS) [11]. The TGR measures the continuous changes of tumor size longitudinally and thus may reflect the tumor kinetics more precisely. In the pre-treatment period of the CLARINET trial the TGR was 2.7% per month in the placebo arm and the growth dynamic did not change within the observational period of 96 weeks. In practice, two imagings are mandatory to calculate the TGR correctly. In order to determine whether the W&W strategy is an appropriate treatment option, the first control imaging should be performed after 3-6 months.

Overall, the TGR provides the opportunity to monitor a W&W strategy and to early predict PFS. Our observation of the W&W strategy in the survey is restricted by a number of limitations. All the participants were patients, which had to understand and recognize the difference between surveillance, drug treatment and watch-and-wait concept. No definition of W&W was provided. The survey did not distinguish between localized and metastatic stages. Therefore, the proportion of patients with e.g. gastric NET type 1 or non-functional small PanNET, where W&W is regular performed, cannot be indicated. Interestingly, some patients under W&W also reported a functional-active and symptomatic disease both representing indications for therapy. This discrepancy cannot be explained definitively.

Nevertheless, we would like to raise awareness that a W&W concept is still a valuable option for NET patients. Further scientific attention should be directed towards the clinical and molecular characterization of indolent and very slow-growing NET in order to better select patients.

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