J Med Drug Rev 2014;4:27–34

Oral vinorelbine for the treatment of breast cancer and non-small cell lung carcinoma in clinical practice

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Summary

Vinorelbine is an established chemotherapeutic agent used for the treatment of patients with metastatic breast cancer and non-small cell lung carcinoma. An oral formulation of vinorelbine is available, which is equivalent in efficacy to the i.v. drug but is preferred by patients. To further optimize treatment with oral vinorelbine, three non-interventional studies (Online, Chrono and Time&Motion NIS) were conducted between 2008 and 2011 in Germany. These studies assessed the efficacy and tolerability of oral vinorelbine in routine clinical practice. The specific objectives of the individual studies were: (1) correlation of gastrointestinal toxicities with time of day of drug intake and evaluation of concomitant antiemetic treatment; (2) analysis of the length of time required for various operational procedures and waiting times using oral or intravenous vinorelbine; (3) assessment of patient and physician satisfaction with treatment. The results obtained in the three NIS confirmed the good efficacy and tolerability of oral vinorelbine in clinical routine practice, which is also reflected by the high level of treatment satisfaction expressed by patients and physicians.

Keywords: Breast cancer · NSCLC · chemotherapy · palliative therapy · oral vinorelbine

1. Introduction

Non-small cell lung cancer (NSCLC) and breast cancer (BC) are among the three most common types of cancer, accounting for 43 % of the new estimated cases in women and 14 % in men.[1] One of the cornerstones in the treatment of these cancers is chemotherapy. In the early stages of the diseases the prime requirement for chemotherapy is its efficacy. In the advanced stages the main aims of chemotherapy are to prolong survival, maintain quality of life and control symptoms,[2,3] and these criteria determine the choice of therapy. Thus, in addition to efficacy, the spectrum of adverse effects and the wishes of the individual patient should be taken into consideration when choosing treatment for palliation.

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The cytotoxic agent vinorelbine is well established as single agent or combination therapy for the treatment of stage III and IV NSCLC and stage IV BC. Vinorelbine belongs to the class of vinca alkaloids, which have an antiproliferative effect by inhibiting the function of microtubules during mitotic cell division.[4] The efficacy of vinorelbine has been investigated in numerous studies. In first-line therapy of metastatic BC, overall response rates ranged from 41 % to 60 %, and for advanced NSCLC from 12 % to 42 %.[5,6,7] Vinorelbine is generally well tolerated. Stigmatizing adverse effects such as hair loss are less common than with other cytostatics. The main toxicity is related to the bone marrow (leukopenia, neutropenia and anemia). Gastrointestinal symptoms may occur but can be reduced or prevented by adequate antiemetic medication.[8,9]

Vinorelbine is available as an intravenous (i.v.) and oral (Navelbine® Oral) formulation. The efficacy and tolerability of the two formulations are comparable, and the relative bioavailability of the oral versus the i.v. formulation is about 40 %, resulting in a reliable dose equivalence (80 mg orally = 30 mg i.v.; 60 mg orally = 25 mg i.v.).[10,11,12,13] The more recently introduced oral form was preferred by 74 % of

the patients who had received both formulations in a crossover study because they felt less ill and could integrate oral treatment better in their daily life.[14] Furthermore, oral therapy lacks the risks associated with venous access and reduces the length of stay in the hospital or in an outpatient setting. Thus, oral administration may provide significant staff time savings.[9,14,15]

The three non-interventional studies (NIS) summarized here were performed to gain further experiences with oral vinorelbine in daily practice and collect data in order to optimize treatment.

2. Methods

2.1 Study designs

The studies were conducted as open, multicenter, prospective, non-interventional, observational surveys. Overall, 161 patients were enrolled between 2008 and 2011 in 51 outpatient oncology practices, hospital-based outpatient oncology clinics or oncology day clinics in Germany. Eligible patients had been diagnosed with advanced NSCLC or with metastatic BC after failure of a prior anthracycline and taxane regimen or where these therapies were not indicated, and all patients were treated with vinorelbine. The treatment plan and objectives of the three studies, "Online", "Chrono" and "Time&Motion", are listed in Table 1. The Online NIS focused on the efficacy and tolerability of oral vinorelbine as single agent and combination therapy. The primary objective of the Chrono NIS was to evaluate gastrointestinal tolerability according to the time of day when oral vinorelbine was taken ("in the morning", "at noon", "in the evening" or "at night"). The Time&Motion NIS was designed to obtain data on the duration of various procedures and waiting times in hospitals and oncology practices associated with intravenous versus oral vinorelbine.

2.2 Physician's and patient's assessments

In the Chrono and Online NIS physicians and patients were asked to assess different aspects of treatment and patients' conditions. Ratings were based on a five to six-point scale (very good to very bad).

2.3 Assessment of gastrointestinal events in relation to the time of day of drug intake

In the Chrono NIS data were recorded using a patient diary. Evaluation was performed on the basis of the number of applications per time window and the number of applications per time window after which a gastrointestinal event occurred. The times of day were defined as follows: "in the morning", 5:00 a.m. to 11:00 a.m.; "at noon", > 11:00 a.m. to < 5:00 p.m.; "in the evening", 5:00 p.m. to 11:00 p.m.; "at night", > 11:00 p.m. to < 5:00 a.m.

2.4 Statistical analysis

Data analysis was performed using descriptive statistics and, in the Online and Chrono NIS, separately for NSCLC and BC patients. Questionnaires for physicians and patients were used. For continuous parameters the number of observations, mean, minimum, median and maximum values, standard deviations and 95 % confidence intervals (CI) were calculated. For categorical parameters, absolute and relative frequencies were determined. Progression-free survival (PFS) and time to progression (TTP) were assessed using the Kaplan-Meier method. The frequencies of nausea at different times of day were compared between the two arms using twotailed Fisher's exact test.

3. Results

3.1 Patient characteristics

For the Online, Chrono and Time&Motion NIS, 57 (35 %), 81 (50 %) and 23 (14 %) evaluable patients were recruited, respectively (Table 2). Of these patients, 105 (65 %) had BC and 56 (35 %) NSCLC. The median age of the total population ranged from 64 to 68 years and the majority of the study population was female (n = 112, 70 %).

The general condition of the most patients was moderate to good (median Karnofsky index 80 – 90 %; median ECOG score 1) while some individuals presented with a markedly impaired health status (minimum Karnofsky index 20 %; maxi-

Table 1: Overview of NIS

	Online	Chrono	Time & Motion
n	**57**	**81**	**23**
Treatment plan	Single agent and combination therapy with oral vinorelbine	Single agent therapy with oral vinorelbine	Single agent and combination therapy with i.v. or oral vinorelbine
Objectives	Tolerability Evaluation of treatment by physicians and patients Concurrent antiemetic treatment		
	Efficacy	Gastrointestinal tolerability depending on the time of day of drug intake	Assessment of time spent during administration of i.v. and oral vinorelbine

Table 2: Patient characteristics according to studies (all non-interventional) and indications

	Online (n = 57)		Chrono (n = 81)		Time&Motion (n = 23)
	BC (n = 36)	NSCLC (n = 21)	BC (n = 51)	NSCLC (n = 31)	BC 78%, NSCLC 17%, unknown 4%; i.v. 78%. p.o. 22%
Median age [years] (range)	64.5 (35.0–85.0)	68.0 (45.0–84.0)	63.5 (43.0–88.0)	71.0 (56.0–85.0)	63.6 (45.1–77.4)
Female [%]	97	24	92	23	87
Median ECOG PS (range)	1 (0–2)	1 (0–3)	–	–	–
Median Karnofsky index [%] (range)	–	–	90 (50–100)	80 (20–100)	90 (60–100)
M0/M1/unknown [%]	8 / 92 / –	14 / 86 / –	10 / 73 / 16	29 / 58 / 13	23 / 64 / 14
Median number of metastatic sites (range)	2 (0–4)	1 (0–3)	–	–	–
Metastatic sites [%]					–
Lung	50	19	32	72	
Bone	36	48	51	6	
Liver	22	14	27	6	
Skin	19	0	3	0	
CNS	6	10	0	17	
Adrenal gland	0	10	0	6	
Other	31	19	35	11	
Prior chemotherapy [%]	83	33	84	65	
Median number of palliative therapy lines (range)	–	–	2 (1–9)	2 (1–9)	–
Therapy line of oral vinorelbine [%]			–	–	–
First-line	17	86			
Second-line	22	0			
Third-line	36	14			
≥ fourth line	25	0			

mum ECOG score 3). Most patients had metastatic disease (M1 58%–92%) usually involving lungs, bone and liver. Accordingly, many patients had received prior chemotherapy, with a median number of one prior palliative treatment line in Chrono NIS. BC patients recruited to the Online NIS had more palliative treatment lines prior to vinorelbine therapy compared with NSCLC patients.

3.2 Exposure

Details on exposure to treatment with vinorelbine are given in Table 3 for the two studies that were analyzed for efficacy and tolerability.

The median number of applications of oral vinorelbine was higher for BC patients than for NSCLC patients in the Online NIS, with a maximum number of 40 cycles. In the Chrono NIS, both BC and NSCLC patients received a median number of 8 applications, which was the maximum observation period. In the Online NIS, oral vinorelbine was administered more often as part of a combination regimen (BC 58%, NSCLC 71%); for BC, the most frequently used combination partners were trastuzumab (24%), bevacizumab (19%), capecitabine (19%) and gemcitabine (19%), and for NSCLC carboplatin (56%) and gemcitabine (19%).

Most of the patients in both studies received concurrent antiemetic treatment (>70%).

Table 3: Exposure to oral vinorelbine (Online- + Chrono NIS)

	Online (n = 57)		Chrono (n = 81)	
	BC (n = 36)	NSCLC (n = 21)	BC (n = 51)	NSCLC (n = 31)
Median duration of therapy [weeks] (range)	15 (1–44)	10 (1–40)	7 (0–12)	7 (3–15)
Median number of applications (range)	12 (1–37)	6 (1–40)	8* (1–8)	8* (3–8)
Type of therapy [%]				
Monotherapy	42	24	94	98
Combination	58	71	6	2
Concomitant antiemetic treatment [%]	86	95	72	90

Time&Motion NIS was not considered because the observation period was limited to one day.
* In the Chrono NIS, observation was limited to a maximum of eight applications.

Table 4: Efficacy of treatment with oral vinorelbine (Online NIS)

	Online (n = 57)	
	BC (n = 36)	NSCLC (n = 21)
Overall response rate [%]*	11	38
Disease control rate [%]	50	48
Median time to progression [mo] (95% CI)**	5.7 (3.8–9.7)	5.4 (2.2–10.8)

* Partial remission in all cases.
** BC: n = 35; NSCLC: n = 12.

Table 5: Most common adverse effects under treatment with oral vinorelbine (> 4%, all grades) (Online + Chrono NIS, n = 138)

	Adverse events (%)	Serious adverse events (%)
Total	51.4	10.9
Nausea	25.4	2.9
Vomiting	17.4	2.2
Anemia	14.5	0
Leukopenia	13.8	1.4
Diarrhea	10.9	0.7
Fatigue/asthenia/malaise	6.5	1.4
Neutropenia	5.8	0
Infection	5.1*	2.2
Thrombopenia	4.3	0
Reduced general condition	3.6	1.4

* Only one case of neutropenic infection (0.7%).

3.3 Efficacy of oral vinorelbine

The efficacy of treatment with oral vinorelbine was assessed in the Online NIS (n = 57) (Table 4). In BC patients (n = 36) the disease control rate (DCR) was 50% and a partial response was achieved in 11%. Median time to progression (TTP) was 5.7 months (95% CI 3.8–9.7). In NSCLC patients (n = 21), DCR was comparable (48%), with more patients responding objectively to treatment (38%). Median TTP was 5.4 months (95% CI 2.2–10.8).

To evaluate the global effectiveness of oral vinorelbine, taking into account individual factors (indication, patient history, pretreatment), the attending physicians were asked for their ratings. The results of this evaluation performed in the Online and Chrono NIS are depicted in Figure 1A. The efficacy was rated as good to very good in half of the patients, as moderate in 28% and as bad in only in 11% of the patients (very bad 0%).

3.4 Tolerability and safety

Treatment with oral vinorelbine was well tolerated (Table 5). Altogether, adverse events potentially related to chemotherapy (all grades) occurred in 51.4% of the patients. As expected, gastrointestinal complaints such as nausea (25%), vomiting (17%) and diarrhea (11%) were among the most frequently reported events. Hematological disorders were primarily anemia (15%), leukopenia (14%), neutropenia (6%) and thrombopenia (4%). Fatigue was documented in 5% of the patients, infections were reported in 4%, but neutropenic infection was seen in only one patient (0.7%); febrile neutropenia was not observed.

Most of the adverse events were mild as reflected in the low number of serious treatment-related events. Overall, 11% of the patients experienced serious adverse events, most frequently nausea (2.9%), vomiting (2.2%), infections (2.2%), fatigue/asthenia (1.4%), leukopenia (1.4%) and reduced general condition (1.4%). Only one death was reported in all three studies (1/161 patients; 0.6%). This patient with NSCLC in the Online NIS experienced a bleeding duodenal ulcer, and a causal relationship to chemotherapy was considered "unlikely".

Again, the attending physicians were asked to rate the tolerability of treatment based on the frequency of adverse events (Figure 1B). In 73% of cases (n = 137), physicians rated the tolerability as good to very good. In 14% of cases, tolerability was rated as moderate and only in 5% as bad to very bad (very bad: 2%).

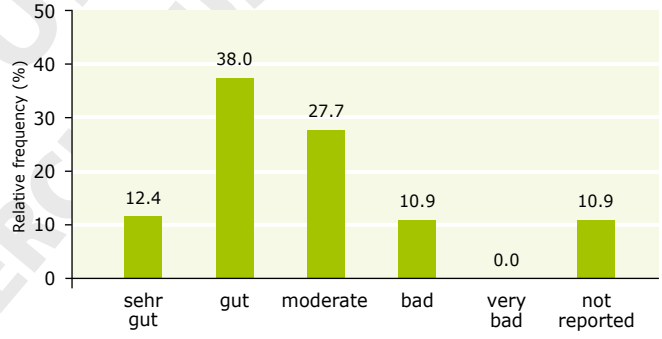
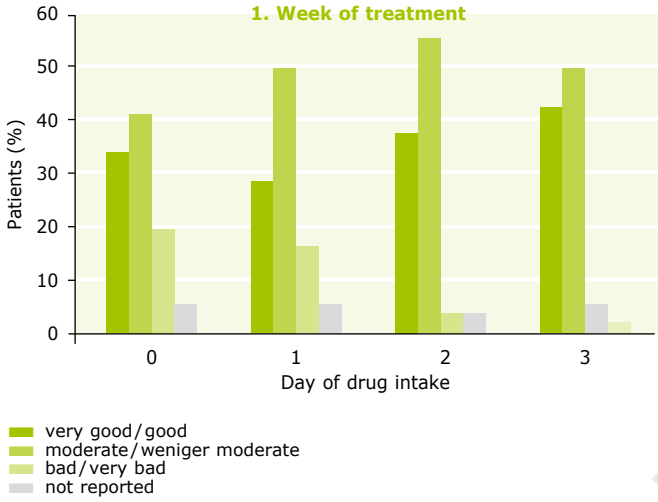


Figure 1A. Evaluation of efficacy by physicians (Online + Chrono NIS, n = 137)

Figure 1B. Evaluation of tolerability by physicians (Online + Chrono NIS, n = 137)



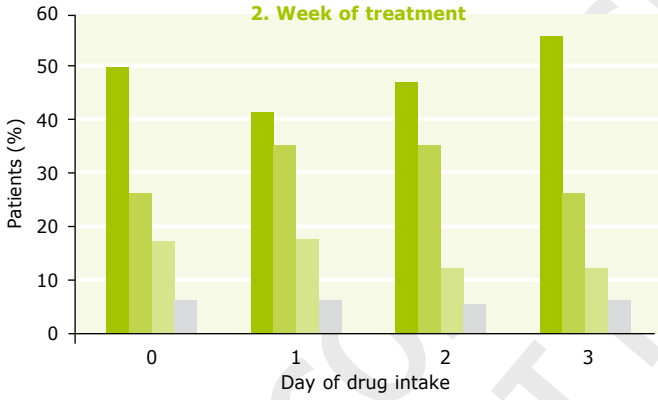


Figure 2. Patient's evaluation of general condition in the first and second week of treatment

3.5 Quality of life

In Online NIS patients were asked to describe their general condition in the first and second week of treatment on the day of taking oral vinorelbine and in the first 3 days following application (Figure 2). Overall, the data show that most patients rated their general condition as very good/good or satisfactory/less satisfactory. On day 1 after treatment the general condition was slightly impaired but improved until day 3. In the BC population it was particularly remarkable that only 2 % of the patients felt bad to very bad as soon as two days after drug intake. In contrast, NSCLC patients tended to feel better on day 0 but the changes were less prominent compared with the BC group.

In addition to the patients' self-assessment, the attending physicians' evaluation of the general condition of the patients at the beginning and end of treatment with oral vinorelbine based on the ECOG performance status (Online NIS) or Karnofsky index (Chrono NIS) was documented. In both studies the median performance status of the BC patients was good (ECOG 1, Karnofsky 90 %) and did not change over the course of treatment (range: ECOG -1.0 to +1.0; Karnofsky -25 % to +25 %). The NSCLC patients had a slightly worse general condition (median ECOG 1, Karnofsky 80 %), with no or minor changes (ECOG 0, range -1.0 to +2.0; Karnofsky index -5 %, range -80 % to +50 %).

3.6 Satisfaction of physicians and patients with oral vinorelbine

Physician and patient satisfaction with oral vinorelbine therapy was evaluated in the Chrono NIS. The evaluation performed at the end of the observation period (n = 80) generally showed a positive assessment of treatment (Figure 3). In 76 % of cases, the attending physicians were satisfied (50 %) to very satisfied (26 %) with oral vinorelbine treatment. This is consistent with the patients' evaluation, who reported to be satisfied to very satisfied with treatment in more than 77 % of cases. In almost all cases (93 %), the attending physicians said that they intended to use oral vinorelbine again (not reported in 5 %).

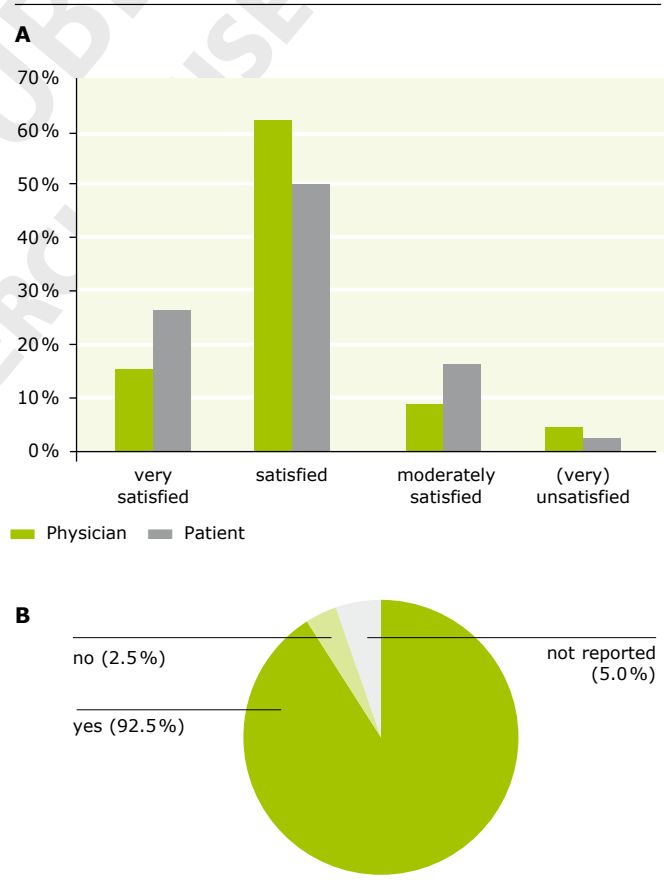


Figure 3. Patient and physician satisfaction with oral vinorelbine treatment (**A**); Physicians' intent to use oral vinorelbine again (**B**) (Chrono NIS)

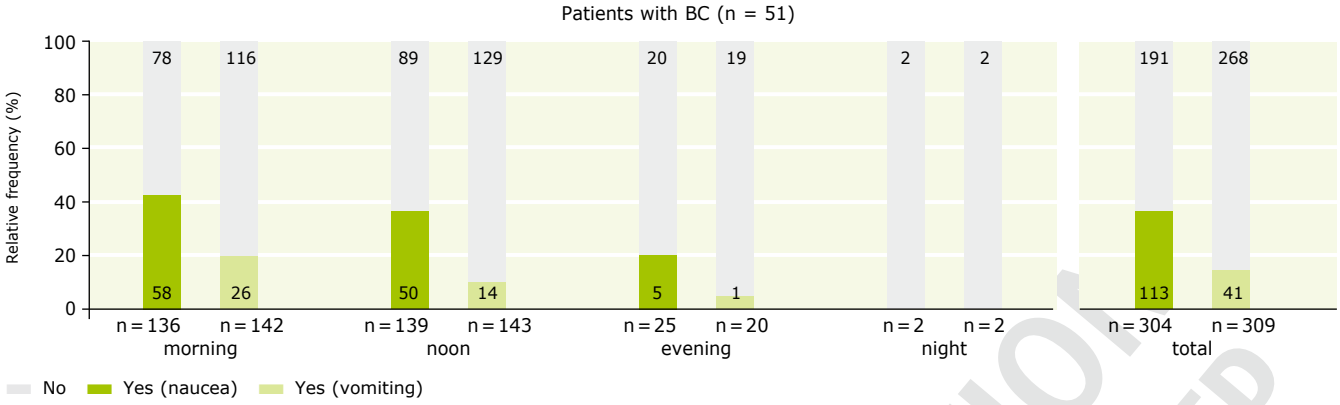


Figure 4. Occurrence of nausea and vomiting within 24 h after taking oral vinorelbine in patients with breast cancer (Chrono NIS)

3.7 Gastrointestinal tolerability in relation to the time of day of drug application

To further improve the tolerability of oral vinorelbine, the Chrono NIS adressed the question whether an optimal time of day for drug intake exists in order to reduce the frequency and grade of nausea and vomiting.

In the BC population most drug applications occurred during the first half of the day (Figure 4). The incidence of vomiting was generally lower than the incidence of nausea. Interestingly, differences were found in the incidence of nausea within 24 hours of taking oral vinorelbine in relation to the four investigated time windows. Nausea occurred after 43 % of the applications in the morning (58/136 evaluable applications); at noon, the incidence was 34 % (50/139 applications) and in the evening 20 % (5/25 applications). Taking the vinorelbine capsules in the evening was associated with significantly less nausea compared with the drug intake in the morning ($p = 0.044$). Generally, late administration (evening or night) induced less nausea compared with drug intake early in the day (morning or noon) ($p = 0.037$).

Due to limited data for the NSCLC population regarding the evening and night application (a total of six administrations), an evaluation of the effect of the time of day of administration was not possible in these patients (data not shown).

3.8 Impact of oral vinorelbine on the workflow in hospitals and outpatient unit practices

Another important aspect of a patient's quality of life is the time they spend for treatment, including hospitalization and physician visits. The Time&Motion NIS investigated the time required for various procedures and the waiting times in the hospital or outpatient unit while on intravenous or oral single agent therapy with vinorelbine in 23 evaluable patients. With oral treatment relevant time savings were achieved compared to i.v. administration with regard to the following time intervals: time before application (from arrival to application; 49 min vs. 67 min; 27 % reduction), prescription time (from pharmacy to treatment center; 7 min vs. 25 min; 73 % reduction), the duration

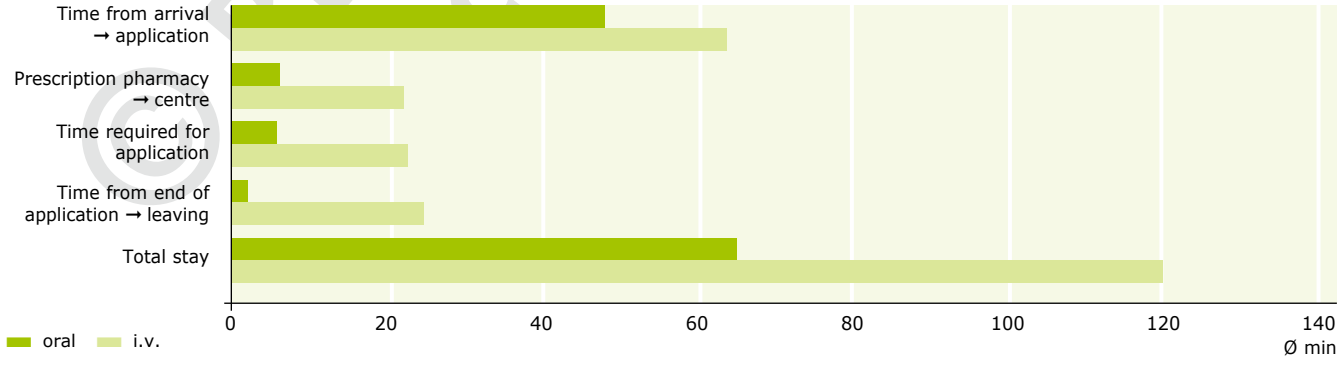


Figure 5. Mean duration of procedures with oral and i.v. vinorelbine (minutes) (Time&Motion); n = 23

of application (6 min vs. 26 min; 76 % reduction) and the period of observation after application (3 min vs. 29 min; 89 % reduction) (Figure 5). Thus, only about half of the time had to be spent for the oral vs. i.v. administration of vinorelbine (67 min vs. 123 min; 46 % reduction).

In addition to the time saving within a medical facility the oral form of vinorelbine also leaves the option of taking the drug at home, which was documented in the Online NIS for 59 % of the patients.

4. Discussion

The three NIS presented here give insight into various aspects of treatment with oral vinorelbine in daily practice.

The purpose of NIS is to collect data on treatment with pharmaceutical preparations by means of epidemiological methods.[16] Thus, this study type plays an important role in health care research.

In the NIS presented here, chemotherapy with oral vinorelbine was investigated in patients with metastatic breast cancer and advanced non-small cell lung cancer under routine conditions in Germany.

Observations referred to an unselected patient population. Analysis of the patient characteristics showed a realistic patient profile: advanced age (median 64 – 71 years), broad range in Karnofsky index (20 – 100 %) and ECOG performance status (0 – 3) respectively, extensive distant metastatic spread (58 – 92 % of patients), extensive prior treatment, especially of the BC patients (previous chemotherapy in up to 84 % of patients), use of oral vinorelbine in higher therapy lines, especially in the group of BC patients (second line in 83 % of patients).

Analyses of the safety data showed an excellent tolerability of oral vinorelbine, which is consistent with previous experiences obtained with this agent.[17] Accordingly, most of the patients (> 75 %) reported a satisfactory to very good general condition during treatment.

However, the results of the Chrono NIS showed that treatment can still be optimized in clinical routine practice. In patients with BC, the data suggest that application of oral vinorelbine in the evening is preferable because it produces fewer gastrointestinal effects. The Chrono NIS indicated that the frequency of nausea can be reduced in BC patients by taking oral vinorelbine at the end of the day rather than in the morning or at noon. A possible explanation could be that mild nausea is not noticed during sleep.

In addition, oral vinorelbine treatment demonstrated good efficacy in this patient population with advanced tumor stages. The results obtained under routine conditions (BC: response rate 11 %, disease control rate 50 %, median PFS 5.6 months; NSCLC: response rate 38 %, disease control rate 48 %, median PFS 4.2 months) are largely consistent with the data collected in clinical studies, although the unselected patient population treated in the NIS cannot be directly compared with the selected populations of clinical trials.[8,14,18,19,20,21]

The results with regard to the tolerability and efficacy of oral vinorelbine were also confirmed by the attending physicians who rated treatment tolerance as good to very good in 73 % and observed clinical efficacy in 50 % of the patients. 76 % of physicians and 77 % of patients reported that they were generally satisfied to very satisfied with treatment. In 93 % of cases, the attending physicians stated that they wanted to use oral vinorelbine therapy again.

These encouraging results are also and particularly related to the oral mode of application of vinorelbine, which is more convenient than intravenous administration that requires frequent venipunctures. Thus oral treatment allows greater personal flexibility and has a positive effect on the patients' quality of life. Compared to i.v. administration, another advantage of oral application is that the patients' length of stay in the oncology practice or the outpatient department can be reduced (67 vs. 123 minutes; 46 % reduction vs. i.v. application).

Conclusions and clinical significance

- Vinorelbine is characterized by excellent tolerability and good efficacy in the treatment of metastatic breast cancer and advanced non-small cell lung cancer.
- The oral formulation of vinorelbine is equivalent in efficacy and tolerability to i.v. vinorelbine and offers additional advantages.
- Oral vinorelbine can be taken by the patient at home, and, if administered in the outpatient setting, may result in considerable time savings both for patients and medical staff in hospitals and outpatient oncology practices compared with the intravenous administration.
- The data suggest that application of oral vinorelbine in the evening may be associated with less nausea and vomiting compared with administration in the morning.
- Overall, the results of the three NIS obtained under clinical routine conditions support the use of oral vinorelbine for the treatment of metastatic breast cancer and advanced non-small cell lung cancer.

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