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SHORT COMMUNICATION

An open label phase 1 study evaluation safety, tolerability, and maximum tolerated dose of oral administration of irinotecan in combination with capecitabine

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Abstract

Purpose Oral administration of chemotherapy offers several advantages in comparison with intravenous administration. Previously, data on a new oral formulation of irinotecan have been published. The aim of the present study was to evaluate the safety, tolerability, and Maximum Tolerated Dose (MTD) of the new oral irinotecan formulation in combination with oral capecitabine.

Methods The study was an open label, phase 1, single center, extension part in which oral irinotecan was investigated in combination with capecitabine. The MTD of irinotecan in combination with capecitabine was 17.5 mg/m^2 once daily for 14 consecutive days in combination with capecitabine 800 mg/m^2 twice daily. Eligible patients were adults with metastatic or unresectable solid tumors for which no standard curative or palliative therapies existed.

Results 14 patients were included in the extension part. No grade 3 or 4 hematologic toxicities were observed. Non-hematological toxicities included grade 1 and 2 diarrhea, fatigue, cholinergic syndrome, vomiting, and weight loss. Totally, 3 grade 3 toxicities and no grade 4 event were reported. No objective responses were observed. Five patients had stable disease lasting median 14 weeks.

Conclusions Capecitabine in combination with oral irinotecan could be a new treatment option offering a more convenient and patient friendly treatment strategy compared to intravenous irinotecan. The combination is fairly tolerated; however, further investigations are needed to assess the efficacy of this regimen.

Keywords Phase 1 study · Oral irinotecan · Capecitabine · Solid tumors

Introduction

Oral administration of chemotherapy offers several advantages in comparison with intravenous administration. Among these are easier administration, the possibility of home treatment, and the facilitation of continuous treatment regimens.

Irinotecan is a topoisomerase inhibitor widely used in the treatment of gastrointestinal cancers. For the treatment of metastatic colon and pancreatic cancers, international guidelines recommend the use of irinotecan in combination with 5-fluorouracil (5-FU) as the first- or second line treatment [1, 2]. For the treatment of metastatic gastric cancer, irinotecan monotherapy is recommended as the second- or third-line therapy [3].

Whereas 5-FU has been available as oral therapy for several years, irinotecan is only marketed as intravenous formulations. During the past years, several attempts have been made to develop a safe and efficacious irinotecan tablet with high bioavailability, low interpatient variability, and acceptable gastrointestinal side effects [4–7]. Despite these efforts, no oral irinotecan formulation has been marketed yet.

Recently, we published data from a phase 1a study on a new oral irinotecan formulation. The formulation is designed as an enteric-coated tablet to allow passage through the stomach before immediate release in the duodenum. This ensures the elimination of one irinotecan dose before

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administration of the next, thus avoiding drug accumulation and ensuring high bioavailability with low inter-patient variability.

In this study, the Maximum Tolerated Dose (MTD) was established at 21 mg/m^2. The most common treatment-related adverse events were nausea and diarrhea which were reported in 58% and 50%, respectively, among patients receiving the MTD. Hematological toxicities were only grade 1 and 2. No complete or partial responses were observed, 9 patients (36%) had stable disease lasting median 19 weeks (range 7–45 weeks).

The study confirmed that the oral irinotecan formulation was indeed rapidly and well absorbed as well as more effectively converted to SN-38 compared to intravenous administration [8].

The aim of the present study was to evaluate the safety, tolerability, and MTD of oral irinotecan in combination with oral capecitabine. This study was conducted as a phase Ib combination study of the previously published phase 1a trial on oral irinotecan given as monotherapy as described above.

Our study consisted of two parts, a dose finding study of the new oral irinotecan formulation as single agent (part a), followed by a study to determine the MTD of oral irinotecan in combination with a fixed dose of capecitabine (part b). As data from part a of the trial has already been published, only data from part b will be presented here.

Patients and methods

Study design

The study was an open label, phase 1a/b, single center, dose-escalating study of a new oral formulation of irinotecan with a part b in which oral irinotecan was investigated in combination with capecitabine. The investigational drug was designed and supplied by Oncoral Pharma ApS Denmark as an enteric-coated immediate release tablet.

The dose of irinotecan in combination with capecitabine was decided to be one dose level below the MTD level of irinotecan as single agent. Based on part a of the study [8], this dose was set at 17.5 mg/m^2 once daily (OD) in the morning, the capecitabine dose was 800 mg/m^2 twice daily (BID). Irinotecan was administered in the free base form thus 17.5 mg/m^2 corresponds to 20.2 mg/m^2 of irinotecan hydrochloride trihydrate. Both irinotecan and capecitabine were given for 14 consecutive days, followed by 1 week off medication in a 3-week treatment cycle. In part b, 12 patients were planned to be included. The first cohort of 3 patients was treated at dose level 1 (17.5 mg/m^2 OD/800 mg/m^2 BID). If this was safe and well-tolerated, the next three patients were to be treated at dose level 2 (21 mg/m^2 OD/ 800 mg/m^2 BID). If this dose was also safe and well tolerated, additional six patients were to be treated at dose level 2. If not considered safe, the remaining six patients were to be treated at dose level 1.

Patients were treated for two consecutive treatment cycles within the study. For ethical reasons, repetition of the treatment cycles beyond the two cycles within the study was allowed until progression, death, or unacceptable toxicity.

Dose-limiting toxicities (DLT) were defined as neutropenia or thrombocytopenia grade 4 or bleeding due to thrombocytopenia, any grade 3–4 adverse event thought to be treatment related, grade ≥ 3 diarrhea, vomiting or nausea despite optimal treatment, moderate-to-severe symptoms of early cholinergic syndrome, or other adverse reactions leading to treatment delay for more than 2 weeks.

All side effects were graded according to the toxicity and response criteria of the Eastern Cooperative Oncology Group version 4.0 [9].

Study population

Eligible patients were adults with metastatic or unresectable solid tumors for which no standard curative or palliative therapies existed. Patients in performance status 0–1 according to ECOG were eligible [9]. Patients with known prior hypersensitivity to either irinotecan or capecitabine were excluded.

Study objectives

The objective was to evaluate safety and tolerability and to determine the MTD of an oral formulation of irinotecan in combination with capecitabine.

Statistical analysis

No formal statistical analyses were performed on safety or efficacy data, as this was a phase 1 study. Descriptive statistics were used for patient demographics, safety, and efficacy data.

Ethics

The study was performed in accordance with the Declaration of Helsinki, ICH-Good Clinical Practice and approved by The Regional Ethics Committee (H-15000878) of Denmark. All included patients provided written, informed consent. The study was initiated by the principal investigator at Herlev and Gentofte Hospital, Department of Oncology and partly sponsored by grants from the Innovation Foundation and The Danish Cancer Society and registered at EudraCT (2014-005584-32) and at ClinicalTrials.Gov (NCT03295084).

Results

Patient characteristics

From June 1st, 2017 to June 7th, 2018, 14 patients were treated in part b of the study. Median age was 69.5 years (range 43–85), eight were performance status (PS) 0, and six were PS 1. Most patients had prostate cancer (8 patients), two patients had rectal cancer, and one each duodenum, bladder, head, and neck cancer and one patient had a neuroendocrine tumor in the colon. Patients had received median 3 numbers of prior treatments (ranges 1–4). Three patients had received irinotecan prior to inclusion, while five patients had received either capecitabine, 5-FU or both.

All patients were treated at the same dose of irinotecan (17.5 mg/m^2). Treatment lasted median 5.9 weeks (range 1.3–19.7 weeks) corresponding to a median of 2 cycles (range 1–6).

Patients characteristics are summarized in Table 1.

Table 1 Patient demographics and disease characteristics (14 patients)

Characteristics	Number of patients (%)
Median age, years (range)	69.5 (43–85)
Gender	
Male	10 (71.4)
Female	4 (28.6)
ECOG performance status	
0	8 (57.1)
1	6 (42.9)
Primary cancer	
Prostate	8 (57.1)
Rectum	2 (14.3)
Duodenum	1 (7.1)
Head and neck	1 (7.1)
Bladder	1 (7.1)
Neuroendocrine tumor (colon)	1 (7.1)
Extent of disease	
Locally advanced	4 (28.6)
Metastatic	10 (71.4)
Median number of prior regimen for advanced disease (range)	3 (1–4)
Prior treatment with irinotecan	
Yes	3 (21.4)
No	11 (78.6)
Prior treatment with capecitabine/5-FU	
Capecitabine	1 (7.1)
5-FU	3 (21.4)
Capecitabine and 5-FU	1 (7.1)
No	9 (64.3)

Dose escalation and dose-limiting toxicities

The dose level of irinotecan (17.5 mg/m^2) OD was one dose level below the MTD established in part a of the study in which irinotecan was given as monotherapy. The dose of capecitabine was fixed at 800 mg/m^2 twice daily. Among the first three patients included, one experienced a DLT of grade 3 diarrhea. As the remaining patients in the extended cohort at the initial dose level experienced several grades 2 toxicities including diarrhea, nausea, vomiting, and abdominal pain, the safety board decided not to increase the irinotecan dose. The MTD for irinotecan in combination therapy was thus established at 17.5 mg/m^2 .

Safety

Hematological side effects were mild and manageable. Anemia grade 1 or 2 was found in 4 patients, while two patients experienced grade 1 leukocytopenia and one patient had thrombocytopenia grade 1. No grade 3 or 4 events were reported (Table 2).

Non-hematological grade 1–2 toxicities included nausea in 12 patients, diarrhea (8), fatigue (7), cholinergic syndrome (7), vomiting (7), and weight loss (6). Apart from the DLT of grade 3 diarrhea, only two grades 3 side effects were reported; one fatigue and one abdominal pain.

Totally four patients discontinued treatment due to toxicities.

Efficacy

No objective responses were observed. Five patients had stable disease (SD), seven had progressive disease (PD), while two patients were non-evaluable. SD lasted median 14 weeks (range 12–29 weeks).

As of October 2018, 10 patients had died.

Discussion

The aim of this study was to determine the MTD of an oral irinotecan formulation in combination with capecitabine. The combination is widely used in the treatment of colorectal cancer and the opportunity to dose both drugs perorally would introduce a patient friendly and convenient treatment strategy allowing for home administration as well as for regimens of more frequent dosing.

Table 2 Treatment-related adverse event (14 patients)

	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	All grade *n* (%)
Fatigue	4 (28.6)	3 (21.4)	1 (7.1)	8 (57.1)
Weight loss	6 (42.9)	0	0	6 (42.9)
Constipation	3 (21.4)	0	0	3 (21.4)
Diarrhea	5 (35.7)	3 (21.4)	1 (7.1)	9 (64.3)
Nausea	6 (42.9)	6 (42.9)	0	12 (85.7)
Vomiting	3 (21.4)	4 (28.6)	0	7 (50.0)
Cholinergic syndrome	6 (42.9)	1 (7.1)	0	7 (50.0)
Mucositis	3 (21.4)	1 (7.1)	0	4 (28.6)
Dyspnea	3 (21.4)	0	0	3 (21.4)
Fever	1 (7.1)	0	0	1 (7.1)
Febrile neutropenia	0	0	0	0
Anemia	3 (21.4)	1 (7.1)	0	4 (28.6)
WBC decreased	2 (14.3)	0	0	2 (14.3)
ANC decreased	0	0	0	0
Platelet count decreased	1 (7.1)	0	0	0
Abdominal pain	4 (28.6)	2 (14.3)	1 (7.1)	7 (50.0)
Palmar-plantar erythrodysesthesia syndrome	3 (21.4)	3 (21.4)	0	6 (42.9)
Other	6 (42.9)	4 (28.6)	0	10 (71.4)

Grade 4/5 adverse events were not observed

We have previously shown that a new oral irinotecan formulation was safe, well absorbed, and fairly tolerated among heavily pretreated patients with solid tumors.

The combination of oral irinotecan and capecitabine has been investigated in few previous studies using different irinotecan formulations.

One study investigated increasing doses of a semi-solid matrix capsule of irinotecan combined with capecitabine. The MTD was found to be 30 mg/m^2 for irinotecan dosed once daily for 14 consecutive days combined with capecitabine 800 mg/m^2 twice daily for 14 days every 3 weeks. Five patients were treated at the MTD level, while 25 patients in total were treated with irinotecan and capecitabine. In the MTD cohort, one patient each experienced grade 3 diarrhea and vomiting. Grade 3 nausea was observed in two patients. No grade 3 or 4 hematologic toxicities were reported. Among 25 patients treated with combination therapy, four patients had a partial response and six patients had stable disease (SD) [6].

Another study investigated the MTD of a semi-solid matrix formulation of irinotecan as a single agent and in sequential combination with capecitabine. The MTD for sequential therapy was established at 40 mg/m^2 irinotecan on days 1–5 and 800 mg/m^2 twice daily of capecitabine days 6–14 in 21 days cycles. In this cohort, 18 patients were included. Hematologic toxicities included one grade 3 anemia and thrombocytopenia each. In addition, non-hematological grade 3 toxicities included vomiting and nausea which occurred in 3 patients each, while one patient experienced grade 3 diarrhea. No patients treated with sequential irinotecan and capecitabine had objective response, but among 40 patients included in the combination cohort, SD was found in 21 patients (52.5%) [10].

Other studies on the combination of irinotecan and capecitabine mainly include studies in which irinotecan was given intravenously. In addition, several different dosing schedules have been used. In the following studies, capecitabine was given at 1000 mg/m^2 twice daily on days 1–14 unless described otherwise [11–15] .

A randomized phase II study comparing irinotecan 80 mg/m^2 days 1 and 8 every 3 weeks plus cisplatin to irinotecan plus capecitabine in patients with advanced non-small-cell lung cancer, reported neutropenia grade 3–4 in 27%, diarrhea in 11% and nausea, and vomiting in 5% of the 37 patients receiving irinotecan and capecitabine [12].

In another study, among 30 patients treated with irinotecan 100 mg/m^2 days 1 and 8 every 3 weeks and capecitabine in the first line for colorectal cancer, grades 3 or 4 diarrhea were reported in 20% of patients, while grade 3 or 4 leukopenia were seen in 23% of patients [11].

A phase II study in 36 heavily pretreated patients with metastatic breast cancer reported neutropenia grade 3 and 4 in 30.6% and 27.8% of patients, respectively. Non-hematologic grade 3 AEs included diarrhea in 8.3% of patients and vomiting in 2.8%. Patients were treated with irinotecan 80 mg/m^2 days 1 and 8 every 3 weeks and capecitabine [13]. A recent study including 221 patients with metastatic breast cancer compared irinotecan 80 mg/m^2, days 1 and 8

and capecitabine to capecitabine monotherapy 1 ,250 mg/m^2 twice daily on days 1–14 every 3 weeks. In the combination arm, hematological toxicities grades 3 and 4 were observed in 60 patients (54%), while grade 3 or 4 diarrhea was reported in 3 patients (2.7%) [14].

Another study in 52 patients with metastatic colorectal cancer used a regimen of irinotecan 250 mg/m^2 on day 1 and capecitabine. Grade 4 toxicities were reported in 27% of patients, mainly neutropenia (15.4%), while 20% of patients experienced grade 3 diarrhea [15].

In a phase II study on weekly irinotecan 90 mg/m^2 and capecitabine given at 1200 mg/m^2 days 1–5, the overall incidence of grade 3–4 AEs was 55.5%, severe diarrhea was reported in 7.7% of study participants and included one grade 4 diarrhea [16].

In a study with a similar design, except irinotecan was given at 240 mg/m^2 no diarrheas and only grade 1 toxicities were reported [17].

Recently, data from a modified regimen of capecitabine and irinotecan for the treatment of metastatic colorectal cancer were published. Irinotecan was given intravenously 200 mg/m^2 on day 1 along with capecitabine 800 mg/m^2 twice daily on days 1–4 every 3 weeks. Grades 3 and 4 neutropenia were reported in 16% of patients, diarrhea grade 3 in 7% (no grade 4 events reported), and vomiting in 2% of patients. These data included patients treated with irinotecan and capecitabine ± bevacizumab, as data were not provided for patients receiving irinotecan and capecitabine only [18].

The different doses and treatment schedules of irinotecan along with the fact that these studies used intravenous irinotecan make any direct comparisons on toxicity impossible. Hematologic toxicities grades 3 and 4 were reported in 23–60%, while diarrhea was reported in 2.7–20% and grade 3 vomiting in 2.8–5%.

In our study, no grade 3 or 4 hematologic events were reported, and only one grade 3 diarrhea (7.1%) and no grade 3 vomitings were observed.

The incidence of grade 3 or 4 diarrhea among patients treated with intravenous irinotecan in combination with 5-FU is reported to be 11–14% [19]. Compared to this, we found only one grade 3 diarrhea corresponding to 7.1% of patients receiving oral irinotecan with capecitabine.

Compared to other published studies on oral irinotecan and capecitabine, our MTD of 17.5 mg/m^2 was lower, although this dose of irinotecan as free base corresponds to 20 mg/m^2 of irinotecan hydrochloride, trihydrate. This could influence the numbers of severe gastro intestinal toxicities.

The present extension study has confirmed the relatively favorable toxicity profile of oral irinotecan in combination with capecitabine. Based on data from other, not directly comparable studies, the safety profile of our oral formulation in combination with capecitabine seems to be at least as favorable as other combination regimens including irinotecan intravenously or oral and capecitabine. Regarding efficacy, this study included various tumor types not very likely to respond to irinotecan. This might be considered a limitation of the study design. Thus, as the number of patients in our study is very small and does not include the patient population most likely to respond to irinotecan, additional studies are required to gain more knowledge regarding toxicities and to establish the efficacy of this regimen.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D, Group EGW (2014) Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 25(Suppl 3):iii1–i9. https://doi.org/10.1093/annonc/mdu260
2. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, Seufferlein T, Haustermans K, Van Laethem JL, Conroy T, Arnold D, Committee EG (2015) Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 26(Suppl 5):v56–68. https://doi.org/10.1093/annonc/mdv295
3. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, Committee EG (2016) Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-Ann Oncol 27(suppl 5):v38–v49. https://doi.org/10.1093/annonc/mdw350
4. Berlin J, Benson AB, Rubin EH et al (2003) Phase I safety, pharmacokinetic and bioavailability study of a semi-solid matrix formulations of oral irinotecan i pateitns with advanced solid tumors. Proc Am Soc Clin Oncol 22:130 (**abstract 521**)
5. Dumez H, Awada A, Piccart M, Assadourian S, Semiond D, Guetens G, de Boeck G, Maes RA, de Bruijn EA, van Oosterom A (2006) A phase I dose-finding clinical pharmacokinetic study of an oral formulation of irinotecan (CPT-11) administered for 5 days every 3 weeks in patients with advanced solid tumours. Ann Oncol 17(7):1158–1165. https://doi.org/10.1093/annonc/mdl071
6. Kuppens IE, Dansin E, Boot H, Feger C, Assadourian S, Bonneterre ME, Beijnen JH, Schellens JH, Bonneterre J (2006) Dose-finding phase I clinical and pharmacokinetic study of orally administered irinotecan in patients with advanced solid tumors. Clin Cancer Res 12(12):3774–3781. https://doi.org/10.1158/1078-0432.CCR-05-2368
7. Schoemaker NE, Kuppens IE, Huinink WW, Lefebvre P, Beijnen JH, Assadourian S, Sanderink GJ, Schellens JH (2005) Phase I study of an oral formulation of irinotecan administered daily for 14 days every 3 weeks in patients with advanced solid tumours. Cancer Chemother Pharmacol 55(3):263–270. https://doi.org/10.1007/s00280-004-0874-2
8. Kumler I, Sorensen PG, Palshof J, Hogdall E, Skovrider-Ruminski W, Theile S, Fullerton A, Nielsen PG, Jensen BV, Nielsen DL (2018) Oral administration of irinotecan in patients with solid tumors: an open-label, phase I, dose escalating study evaluating

safety, tolerability and pharmacokinetics. Cancer Chemother Pharmacol. https://doi.org/10.1007/s00280-018-3720-7
9. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5(6):649–655
10. Goff LW, Benson AB III, LoRusso PM, Tan AR, Berlin JD, Denis LJ, Benner RJ, Yin D, Rothenberg ML (2012) Phase I study of oral irinotecan as a single-agent and given sequentially with capecitabine. Invest New Drugs 30(1):290–298. https://doi.org/10.1007/s10637-010-9528-x
11. Assy N, Basher W, Chetver L, Shnaider J, Zidan J (2012) First-line treatment with capecitabine combined with irinotecan in patients with advanced colorectal carcinoma: a phase II study. J Clin Gastroenterol 46(4):e27–e30. https://doi.org/10.1097/MCG.0b013e3182470f09
12. Han JY, Nam BH, Kim HY, Yoon SJ, Kim HT, Lee JS (2012) A randomized phase II study of irinotecan plus cisplatin versus irinotecan plus capecitabine with or without isosorbide-5-mononitrate in advanced non-small-cell lung cancer. Ann Oncol 23(11):2925–2930. https://doi.org/10.1093/annonc/mds122
13. Lee KS, Park IH, Nam BH, Ro J (2013) Phase II study of irinotecan plus capecitabine in anthracycline- and taxane- pretreated patients with metastatic breast cancer. Invest New Drugs 31(1):152–159. https://doi.org/10.1007/s10637-012-9824-8
14. Park IH, Im SA, Jung KH, Sohn JH, Park YH, Lee KS, Sim SH, Park KH, Kim JH, Nam BH, Kim HJ, Kim TY, Lee KH, Kim SB, Ahn JH, Lee S, Ro J (2018) Randomized open label phase III trial of irinotecan plus capecitabine versus capecitabine monotherapy in patients with metastatic breast cancer previously treated with anthracycline and taxane: PROCEED Trial (KCSG BR 11 – 01). Cancer Res Treat. https://doi.org/10.4143/crt.2017.562
15. Patt YZ, Lee FC, Liebmann JE, Diamandidis D, Eckhardt SG, Javle M, Justice GR, Keiser W, Salvatore JR, Bexon A, Lin E (2007) Capecitabine plus 3-weekly irinotecan (XELIRI regimen) as first-line chemotherapy for metastatic colorectal cancer: phase II trial results. Am J Clin Oncol 30(4):350–357. https://doi.org/10.1097/COC.0b013e31804b40bb
16. Li W, Xu J, Shen L, Liu T, Guo W, Zhang W, Chen Z, Zhu X, Li J (2014) Phase II study of weekly irinotecan and capecitabine treatment in metastatic colorectal cancer patients. BMC Cancer 14:986. https://doi.org/10.1186/1471-2407-14-986
17. Gennatas C, Michalaki V, Gennatas S, Papalambros E (2008) Irinotecan plus capecitabine as first-line chemotherapy in advanced colorectal cancer. Anticancer Res 28(3B):1923–1926
18. Xu RH, Muro K, Morita S, Iwasa S, Han SW, Wang W, Kotaka M, Nakamura M, Ahn JB, Deng YH, Kato T, Cho SH, Ba Y, Matsuoka H, Lee KW, Zhang T, Yamada Y, Sakamoto J, Park YS, Kim TW (2018) Modified XELIRI (capecitabine plus irinotecan) versus FOLFIRI (leucovorin, fluorouracil, and irinotecan), both either with or without bevacizumab, as second-line therapy for metastatic colorectal cancer (AXEPT): a multicentre, open-label, randomised, non-inferiority, phase 3 trial. Lancet Oncol 19(5):660–671. https://doi.org/10.1016/S1470-2045(18)30140-2
19. Stein A, Voigt W, Jordan K (2010) Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management. Ther Adv Med Oncol 2(1):51–63. https://doi.org/10.1177/1758834009355164