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Whole-body hyperthermia in combination with systemic therapy in advanced solid malignancies

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ABSTRACT

Whole-body hyperthermia (WBH) might be beneficial for patients with metastasized solid malignancies when combined with systemic therapy. This review identified and summarized the phase I/II studies (n = 13/14) conducted using this combination of therapies. Most of the phase II studies used radiant heating methods in a thermal dose of 41.8 °C (1 h). All studies used classic chemotherapy. Great inter-study heterogeneity was observed regarding treatment regimes, included patients and reported response rates (12–89%). Ovarian cancer, colorectal adenocarcinoma, lung cancer and sarcoma have been studied most. Most reported toxicity (grade 3/4) was myelosuppression. Treatment related mortality was present (4 patients) in three out 14 phase II studies (350 evaluable patients, over 966 cycles of WBH with chemotherapy). Absence of phase III trials makes the additive value of WBH highly speculative. As modern oncology offers many less invasive treatments options, it is unlikely WBH will ever find its way in routine clinical care.

1. Introduction

1.1. General introduction

Use of hyperthermia as adjunct to existing treatment regimes in cancer therapy is not a new concept. For decades local, regional or whole-body hyperthermia (WBH) has been applied in a wide variety of different combinations with chemotherapy or radiotherapy (Falk and Issels, 2001; Moyer and Delman, 2008; Peeken et al., 2017; Zee, 2002; Wust et al., 2002). The therapeutic benefit of locoregional hyperthermia as adjunct to radiotherapy or chemotherapy for specific indications has undisputedly been determined by several systematic reviews and meta-analyses (Datta et al., 2016a, b; Hu et al., 2017; Lutgens et al., 2010). Recently, also proof of benefit on long-term outcomes of regional hyperthermia combined with chemotherapy has been obtained in patients with localized high-risk soft tissue sarcoma, with a 10-year overall survival rate of 52.6% (95% CI 44.7–60.6%) for chemotherapy with hyperthermia, versus 42.7% (95% CI 35.0–50.4%) for chemotherapy alone (Issels et al., 2018). Similar proof of benefit was found for the use of hyperthermia in combination with intravesical chemotherapy in the treatment of non-muscle invasive bladder cancer (Colombo et al., 2011) and hyperthermic intraperitoneal chemotherapy in the treatment of peritoneal metastasis of ovarian cancer (Driel et al., 2018).

This beneficial effect of locoregional hyperthermia raises the question whether hyperthermia applied to the whole body might be a relevant adjunct to systemic therapy for patients with metastasized or advanced malignancies. However, in contrast with the proven benefits for local and regional hyperthermia, convincing evidence of benefit of WBH, alone or as adjunct to systemic therapy, is lacking.

1.2. WBH induction techniques

To artificially raise the body temperature by exogenously applied heat, two techniques have been used most often over the years, generally aiming at core body temperatures of 41–42 °C (sometimes referred to as extreme WBH) or 39–40 °C (fever-range WBH).

Firstly, several systems have been developed to apply WBH by radiant heat. These systems use non-ionizing, electromagnetic radiation (e.g., infrared, microwave) to heat the body surface/tissues to a certain depth (depending on the used radiation) upon which the skin circulation transports the heat to the body core. Typical time to reach core body temperatures of 41–42 °C is 60–90 minutes and these are maintained for 1–2 h using this method (Hildebrandt et al., 2005; Jia and Liu, 2010; Wust et al., 2002). Often patients were encased in high-humidity cabinets to prevent heat loss by evaporation. Secondly, WBH can be induced by heating the blood in an extracorporeal circulation. The earliest studies describing this technique used a surgical arteriovenous

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shunt as vascular access (Parks et al., 1979). Although very efficient in elevating the core body temperature, this invasive procedure bears the risks of infection and causes a heavy cardiac burden. More recent, extracorporeal WBH techniques using a venovenous circulation have been developed and have been proven a feasible method of safe and effective elevation of core body temperatures (Locker et al., 2011; Zwischenberger et al., 2004).

Both induction methods have been applied in clinical studies in the field of oncology as stand-alone method or combined with chemotherapy and/or radiotherapy.

1.3. Rationale of hyperthermia combined with systemic therapy

The combination of hyperthermia and classic chemotherapy as systemic therapy has been studied most extensively. Mechanisms of cancer inhibition of this combination are twofold: stand-alone malignant cell killing by hyperthermia and chemotherapy potentiation (Hildebrandt et al., 2002; Hurwitz and Stauffer, 2014).

Regarding the first, heat induced apoptosis and mitotic catastrophe are leading mechanisms of cell death upon heat exposure. The surviving fraction of cells is highly dependent on the height of temperature elevation and duration of heat exposure. At the relatively mild temperatures achievable during WBH (up to 42 °C) exponential cell killing will be followed by a plateau level at which cells develop resistance to thermal cell killing (thermotolerance) (Hildebrandt et al., 2002; Roti Roti, 2008). These processes are highly dependent on cell type and the local environment, such as acidity, oxygen status (therapy-resistant hypoxic cells are more thermosensitive) and phase of cell cycle (S-phase being the most thermosensitive). Thermotolerance, although highly dependent on several factors, is generally present after one hour, reaches its maximum after 16 h and is faded out after 120 h, e.g., in the example of 30 min of hyperthermia at 43.5 °C in a C3H mammary carcinoma model (Dewey, 1994; Overgaard and Nielsen, 1983). Among others, complex heat induced alterations in cellular membrane and cytoskelet stability, nuclear protein integrity, cell cycle progression, DNA replication and DNA repair mechanisms are believed to lead to this heat induced cell death (Hildebrandt et al., 2002; Hurwitz and Stauffer, 2014; Kampinga, 2006; Oei et al., 2015; Roti Roti, 2007, 2008). Of special interest is the role of the heat-shock proteins (HSP) in this context. These molecular chaperones play an essential role in protecting the cell to thermal stress by maintaining protein homeostasis and facilitating DNA repair mechanisms. Intracellular HSP concentrations are elevated upon exposure to heat stress, leading to thermotolerance and other forms of cancer therapy resistance (Richter et al., 2010; Sottile and Nadin, 2018; Wu et al., 2017).

In addition to the abovementioned cell-killing capacities of hyperthermia, tumor specific immune reactions can also be induced by hyperthermia, one of which involves heat shock proteins (Frey et al., 2012a; Repasky et al., 2013). HSPs can activate natural killer cells, and extracellular present HSPs can bind tumor antigen and transfer these antigens to antigen-presenting cells (APC), upon which those APCs cross-present them to $CD8^+$ T-cells, thereby eliciting a tumor specific immune reaction (Toraya-Brown and Fiering, 2014). These immune effects have proven hard to exploit clinically so far, however.

The second mechanism for the beneficial effects of the combination of WBH and chemotherapy is chemopotentiation. The magnitude and presence of this effect differs very much between different chemotherapeutics. At the relative mild temperatures achievable during WBH the most thermal enhancement is seen for alkylating agents, platinum containing drugs and nitrosureas, with linear enhancement of cytotoxicity as temperature rises (Bergs et al., 2007; Kampinga, 2006; Urano et al., 1999; Urano and Ling, 2002). Mechanisms of the synergy between chemotherapy and hyperthermia also differ between the different chemotherapeutics (Issels, 2008). One important chemosensitizing feature of hyperthermia is the capability of making chemotherapy induced sublethal cell damage lethal by inhibition of repair mechanisms, e.g. inhibition of DNA repair mechanisms (as mentioned above) (Oei et al., 2015). For example, in vitro, hyperthermia inhibits the enzyme poly ADP ribose polymerase (PARP) in BRCA-competent cells as effective as registered pharmacologic PARP-inhibitors, thereby enhancing delay in DNA repair (Schaaf et al., 2016) and hyperthermia inhibits the homologous recombination DNA repair mechanism by degrading BRCA2 (Krawczyk et al., 2011). The clinical relevance of this inhibitory effect on DNA repair, relevant for both radio- and chemosensitization, was demonstrated in a retrospective analysis which showed higher rates of overall survival in cervical cancer patients when time interval between hyperthermia and radiotherapy was shorter and DNA damage was thereby not yet repaired (Oei et al., 2017; Leeuwen et al., 2017). Hyperthermia also enhances transmembrane transport of chemotherapeutic agents and is reported to cause reperfusion of poorly perfused, treatment resistant tumor regions, thus yielding an indirect but clinically highly relevant mechanism of chemotherapy potentiation, particularly in treatment resistant tumor regions (Dewhirst et al., 2005; Jones et al., 2004; Song et al., 2005).

1.4. Aim of this review

It has not been elucidated whether the potential benefits of the combination of WBH with systemic therapy outweigh the risks associated with either the WBH procedure itself or the possible potentiating of systemic therapy related side-effects, since no randomized phase III trials have been performed. This review aims to address this question by providing a balanced overview of the potential benefits and risks, reported in clinical trials, of WBH in combination with systemic therapy.

2. Methods

2.1. Search strategy

A search strategy combining synonyms of whole-body hyperthermia with synonyms for systemic therapy was conducted in Pubmed, Embase and Web of Science on August 1st 2018 (supplementary Table 1).

2.2. Inclusion criteria

Included articles had to report on efficacy and/or toxicity of WBH (not local/regional hyperthermia) in combination with one or more antineoplastic agent(s) in adult human. The included patients had to suffer from (locally) advanced or metastasized solid malignancies not amenable to curative treatment. Trials eligible for patients with hematological malignancies were only included if results of the patients with solid malignancies were reported separately in the paper. Trials with study interventions other than WBH in combination with systemic therapy (e.g., WBH alone or in combination with surgery/radiotherapy) were included if the main intervention was WBH in combination with systemic therapy and the results of the group receiving systemic therapy were reported separately. There were no restrictions in WBH induction technique, used antineoplastic agents or sequence of WBH/systemic therapy. Articles had to contain original research, had to include more than 1 patient (no case reports) and had to be full text available in English language.

2.3. Data synthesis

Studies included in this review were separated in two groups based on the included patients. Those performed in a population suffering from different malignancies (phase I) and those performed in patients suffering from a specific malignancy (phase II). When reported as such, efficacy was displayed using Response Evaluation Criteria in Solid Tumors (RECIST). In studies including hematological malignancies and allowing other interventions than WBH plus systemic therapy, which did not report a separate proportion of responding patients with solid

Table 1
Yield of search strategy conducted on August 1 2018.

Step		Records
Identification	Database searching Pubmed	248
	Database searching Embase	316
	Database searching Web of Science	676
	Snowballing	1
	Records after duplicates removed	929
Screening	Records screened by title/abstract	929
	Not applicable	876
Eligibility	Full-text articles assessed for eligibility	53
	Excluded after full text assessment	25
	Studies included in review	27

malignancies treated with WBH plus systemic therapy, this number was calculated manually. Whenever possible, grade 3 and 4 toxicity was displayed (World Health Organization/Common Terminology Criteria for Adverse Events), again for the proportion of patients treated with WBH plus systemic therapy. If studies did not grade toxicity, all toxicity was displayed. Regarding mortality, only treatment related mortality was displayed (either from WBH, systemic therapy or the combination).

3. Results

The search strategy in Embase, Pubmed and Web of Science yielded in 929 records after removal of duplicates. After screening on title and abstract on the abovementioned criteria, 53 full-text articles were screened, of which 27 were considered eligible for inclusion in this review (Table 1). Thirteen out of these 27 studies were phase 1 studies, combining WBH with systemic therapy in a population of patients suffering from various malignancies (Bremer et al., 2001; Bull et al., 2008; Gerad et al., 1983, 1984; Herman et al., 1982; Larkin, 1979; Maeta et al., 1987; Ostrow et al., 1981; Pettigrew et al., 1974; Robins et al., 1993, 1999; Robins et al., 1997; Wiedemann et al., 1994). The vast majority of these phase I trials have been performed decades ago in the early days of clinical application of WBH. Supplementary Table 2 lists the characteristics and results of these 13 studies, which show a great diversity regarding study design and outcome.

The remaining 14 studies combined WBH with systemic therapy in patients with a specific malignancy (phase II). For ovarian cancer (n = 3 (Atmaca et al., 2009; Douwes et al., 2004; Westermann et al., 2001)), colorectal cancer (n = 2 (Hegewisch-Becker et al., 2002; Hildebrandt et al., 2004)), lung cancer (n = 2 (Engelhardt et al., 1982; Neumann et al., 1982)) and sarcoma (n = 3 (Bull et al., 1992; Westermann et al., 2003; Wiedemann et al., 1996)) more than one trial has been performed. Single studies are available for cervical cancer (Richel et al., 2004), pancreatic cancer (Bakshandeh-Bath et al., 2009), melanoma (Engelhardt et al., 1990) and pleural mesothelioma (Bakhshandeh et al., 2003) (Table 2). The vast majority of these studies induced WBH using radiant heat (with different radiant heat systems), with an aimed thermal dose of 41.8 °C for 1 h. All studies used classic chemotherapeutic agents as systemic therapy. Used chemotherapeutic regimes differed, however most studies used at least a platinum containing agent (n = 10) or an alkylating agent (n = 6). In most studies pretreatment with chemotherapy was no ground for exclusion, most studies even required some form of chemotherapy pretreatment.

3.1. Phase II studies: efficacy

The combination of WBH with different chemotherapeutics led to response rates (complete response and partial response) varying from 12 to 89% in generally small populations over all the trials. Three studies have been performed in patients with recurrent or platinum resistant epithelial ovarian cancer (58 patients receiving chemotherapy + WBH in total). Observed response rates varied between 38–45% (complete responses + partial responses). Of note, some complete responses were observed in platinum resistant patients treated with carboplatin or cisplatin combined with WBH. In metastatic colorectal cancer two studies have been performed (Hegewisch-Becker et al., 2002; Hildebrandt et al., 2004). *Hegewisch-Becker et al* found a response rate of 20% (56% stable disease, median time to progression of 21 weeks (95%-CI 17–25 weeks)) in patients with advanced colorectal adenocarcinoma after treatment with oxaliplatin, 5-fluoruracil and leucovorin alternated with or without WBH (Hegewisch-Becker et al., 2002). These patients were pretreated with irinotecan or 5-fluoruracil (and leucovorin) or both. Studying the same population (metastatic colorectal adenocarcinoma *Hildebrandt et al* found that 27% of patients not responding to treatment with 5-fluoruracil, folinic acid and mitomycin converted from stable disease to partial response after addition of WBH (combined with hyperoxemia and hyperglycemia) to these agents (Hildebrandt et al., 2004). This result has to be interpreted with caution as only 25 treatment cycles of WBH with chemotherapy were applied in 10 patients. In small cell lung carcinoma two small studies (N = 15 and 18) were perfomed, but these studies are old (both published in 1982) and lack description of pretreatment. This limits drawing of firm conclusions from the reported high response rates (86–89%) (Engelhardt et al., 1982; Neumann et al., 1982). Three studies evaluated the efficacy of WBH in addition to chemotherapy (ifosfamide, carboplatin, etoposide in two out of three) in sarcoma (Bull et al., 1992; Westermann et al., 2003; Wiedemann et al., 1996); thus the malignancy in which WBH is studied in the largest group of patients (in total 124 evaluable patients). The largest study was a multicenter study with 95 evaluable patients. In these patients, suffering from advanced-progressive soft tissue sarcoma (not amenable to local treatment with curative intent or metastatic disease) a response rate was achieved in 28% and stable disease in 33% of patients with a combination of ifosfamide, carboplatin, etoposide and WBH (Westermann et al., 2003). Time to treatment failure was 123 days (95% confidence interval (CI) 77–164) and overall survival 327 days (95%-CI 393–496).

Table 2 summarizes study characteristics, observed response rates and survival in all 14 included phase II studies.

3.2. Phase II studies: toxicity

Serious toxicity (grade 3 or 4) was reported in almost all studies, although the oldest studies did not report any (serious) toxicity or did not grade it. In the studies grading toxicity according to the common criteria for adverse events (CTCAE), the most frequently reported grade 3 and 4 toxicity was myelosuppresion (grade 3 or 4 anemia 5–49%, leukopenia 14–100%, thrombocytopenia 5–65%) in studies with various used chemotherapeutics. Toxicity attributed to WBH occurred less frequently, but serious toxicity (grade 3 an 4), such as ventricular cardiac arrhythmias, dermal complications and kidney failure did occur in several trials. Table 3 lists all observed grade 3 and 4 toxicities.

All studies combined report on at least 966 cycles of WBH plus chemotherapy (not every study reported the total amount of cycles). In these 966 cycles, 4 patients died of treatment related complications on a total of 350 evaluable patients in all studies (161 evaluable patients in the 3 studies reporting mortality (Bakhshandeh et al., 2003; Hegewisch-Becker et al., 2002; Westermann et al., 2003)). All these patients died due to infectious complications (sepsis).

4. Discussion

In this article 27 studies combining WBH with one or more antineoplastic agent(s) were identified, of which 14 studied WBH with systemic therapy in a specific malignancy (phase II). All studies used classic chemotherapy as systemic therapy. The WBH induction technique used in the vast majority of cases was the radiant heating technique. Ranges of target core body temperatures narrowed over time, with 41.8 °C as target temperature in most of the conducted phase II

Table 2
Phase II studies combining whole-body hyperthermia with systemic therapy sorted by tumor type: study design and efficacy.

Study	Tumor type/disease stage	CT Pretreatment	N (included number [1])	Maximal cycles	Antineoplastic agent(s)	WBH method	Thermal dose	Response	Median OS	Median PFS/ TTP
	Gynaecological cancer									
(Atmaca et al., 2009)	Reccurent epithelial ovarian cancer	Yes	47 (35)	6	Carboplatin	R	41.8 °C, 1 hour	CR 11%, PR 34%, NC 26%, PD 29%	61.5 weeks (range: 5-292)	28 weeks (range: 14-172)
(Douwes et al., 2004)	Reccurent epithelial ovarian cancer	Yes, platinum based	21	6	Cisplatin or carboplatin, induced hyperglycemia	R	41.5 – 42 °C, 90 ± 30 minutes	CR 5%, PR 33%, SD 48%, PR 14%	16.5 months (range 6-38)	6.5 months (range 2-24)
(Westermann et al., 2001)	Platinum resistant epithelial ovarian cancer	Yes, platinum based	14 (12)	6	Carboplatin	R	41.8 °C, 1 hour	CR 8%, PR 33%, SD 33%, PD 25%	n.s.	n.s.
(Richel et al., 2004)	Locally advanced or disseminated cervical cancer	Allowed, CT pretreatment in 24%	25 (21)	6	Carboplatin	R	41.8 °C, 1 hour	CR 5%, PR 29%, SD 43%, PD 24%	7.8 months (range 1.3-43+)	5.3 months (range 0.5-43+)
	Gastro-intestinal cancer									
(Hegewisch-Becker et al., 2002)	Colorectal adenocarcinoma, metastatic disease	Irinotecan, leucovorin + 5-fluoruracil or both	44 (41)	12	Oxaliplatin + leucovorin + 5-fluoruracil	R	41.8 °C, 1 hour	CR 5%, PR 15%, SD 56%, PD 22%	50 weeks (95%-CI 39-61)	21 weeks (95%-CI 17-25)
(Hildebrandt et al., 2004)	Colorectal adenocarcinoma, metastatic disease	Limited pretreatment allowed	28 (10)	6 (3 WBH + CT)	5-fluoruracil + folinic acid + mitomycin + induced hyperglycemia + hyperoxemia	R	41.8 °C, 1 hour	After adding WBH: SD → PR 27%, PD → SD 55%	n.s.	n.s.
(Bakshandeh-Bath et al., 2009)	Advanced progressive pancreatic adenocarcinoma	Yes, most	13	n.s.	Gemcitabine + carboplatin	R	41.8 °C, 1 hour	PR 23%, SD 38%	11.4 months	4.7 months
	Lung cancer									
(Engelhardt et al., 1982)	Small cell lung carcinoma, extensive disease	n.s.	15	6	Doxorubicin + Cyclophosphamide + vincristine	R	40.5 °C, 1 hour	CR 53%, PR 33%, NC 7%, PD 7%		n.s.
(Neumann et al., 1982)	Small cell lung carcinoma	n.s.	18	6	Doxorubicin + cyclophosphamide + vincristine	R	40.5 ± 0.5 °C, 1 hour	CR 50%, PR 39%, NC 6%, PD 6%	n.s.	n.s
	Sarcoma									
(Bull et al., 1992)	CT resistant metastatic soft tissue or osteosarcoma	Yes	17	4	Carmustine	C	41.8 – 42.0 °C, 2 hours	PR 12%, OR 24%, SD 6%, PD 59%	4 months (85%-CI 2-12)	5 months (range 2-31)
(Westermann et al., 2003)	Metastatic soft-tissue sarcoma	Allowed, CT pretreatment in 64%	108 (95)	4	Ifosfamide + carboplatin + etoposide	R	41.8 °C, 1 hour	CR 4%, PR 24%, SD 33%, PD 39%	327 days (95%-CI 393-496)	123 days (95%-CI 77-164)
(Wiedemann et al., 1996)	Advanced/metastatic sarcoma	Allowed, CT pretreament in 67%	12	4	Ifosfamide + carboplatin + etoposide	E	41.8 °C, 1 hour	PR 58%, SD 25%, PD 17%	n.s.	n.s.
	Other cancers									
(Engelhardt et al., 1990)	Melanoma	No, except dacarbacin	23 (15)	2	Cisplatin + doxorubicin	R	41 ± 0.5 °C, 45-60 minutes	PR 20%, MR 27%, NC 20%, PD 33%	n.s.	n.s.
(Bakhshandeh et al., 2003)	Non-metastatic advanced pleural mesothelioma	No	27 (25)	3	Ifosfamide + carboplatin + etoposide	R	41.8 °C, 1 hour	PR 20%, MR 12%, SD 44%, PD 24%	76.6 weeks (95%-CI 65-87.8)	29.6 weeks (95%-CI 24.4-34.7)

Abbreviations: N = number of patients, n.s. = not specified, CT = chemotherapy, RT = radiotherapy, WBH = whole-body hyperthermia, CR = complete response, PR = partial response, OR = objective response, MR = minor response, NC = no change. SD = stable disease, PD = progressive disease, R = WBH using radiant heat, E = WBH using an extracorporeal circulation, OS = overall survival, TTP = time to progression, PFS = progression free survival, CI = confidence interval.
Only patients receiving WBH + CT are included in this table and not all patients included in the studies completed follow-up.

studies. All studies achieved objective responses in often heavily pretreated patients, although it remains uncertain which proportion of responses can be attributed to the addition of WBH. Most observed grade 3 and 4 toxicities in the phase 2 studies were attributable to the used chemotherapeutics (e.g., myelosuppression); only a minor proportion to WBH (e.g., dermal, hemodynamic/cardiac complications), although this also concerned serious complications.

Although myelosuppression was the most observed grade 3 or 4 toxicity in the included trials, the proportion of patients with grade 3 or 4 myelosuprresion might have been higher when WBH had not been part of the study intervention. WBH is known to induce the release of several cytokines, including granulocyte stimulating factor (G-CSF), interleukin (IL)-1β, IL-6, IL-8, IL-10 and tumor necrosis factor-α (Robins et al., 1995). It has been postulated that WBH diminishes myelotoxicity of chemotherapeutics through these myeloprotective cytokines, thereby reducing morbidity associated with chemotherapy (Katschinski et al., 1999). This notion was supported by a phase III trial comparing etoposide, ifosfamide and doxorubicin with or without regional hyperthermia in patients with high-risk soft-tissue sarcoma less grade 3 and 4 leucopenia, in which lower percentages of grade 3 and 4 leucopenia were observed in the hyperthermia group than in the control group (63.5% versus 77.6%, $p = 0.005$) (Issels et al., 2010).

Most remarkable of the results reported in this review is the lack of more recently conducted trials on the combination of WBH with systemic therapy, the most recent study was published in 2009. Initiation of a randomized phase III trial, with WBH combined with chemotherapy as experimental arm and chemotherapy alone as control arm, is strongly recommended in many of the phase II studies. However, no results of such randomized trials have been published to date, although two have been registered several years ago: NCT01493011 on 120 stage IIIB/IV non small lung cancer patients (status unknown) and NCT00045461 on 241 patients with recurrent ovarian epithelial, fallopian tube, or peritoneal cancer (status unknown). Lack of unequivocal prove of benefit or disadvantage of WBH as adjunct to chemotherapy which could be provided by such phase III studies is obstructing application of WBH in daily practice. The additive value of this invasive intervention remains therefore highly speculative. Besides this, practical considerations also obstruct widespread application of WBH and can explain the lack of pursuit given to the several phase II studies and the absence of recent studies. One of the most prominent is the elaborate supportive care required for a WBH procedure at 41.8 °C. Minimal requirements for a WBH procedure are: either deep sedation with spontaneous breathing or general anesthesia with intubation, a large bore venous access for aggressive fluid resuscitation (> 1000 ml/h), extensive hemodynamic monitoring and frequent laboratory assessments. Besides this, post-procedure surveillance on an intensive care unit or medium care unit is recommended (Hildebrandt et al., 2005; Locker et al., 2011). This poses logistic problems and makes WBH an expensive and time-consuming procedure. This, combined with the vast evolving and expanding arsenal of antineoplastic agents, i.e. immunotherapy and targeted therapy, available as less invasive treatment option in oncology, makes WBH a less attractive alternative at this stage.

Therefore, the additive value of WBH to classic chemotherapy remains uncertain. Whether WBH could be of benefit when added to other systemic treatment options, such as targeted therapy and/or immunotherapy remains even more speculative. No studies on this combination have been performed so far; all studies included in this review used classic chemotherapy as systemic therapy.

The combination of hyperthermia with targeted therapy or immunotherapy has been scarcely studied in vitro and in vivo for locoregional hyperthermia. Regarding targeted therapy, in vitro hyperthermia enhances effectiveness of dabrafenib and vemurafenib in a melanoma cell line (A375) (Mantso et al., 2018), sunitinib in an adenocarcinoma cell line (MCF-7) (Topcul and Cetin, 2016) and bortezomib in several different cell lines (including MDA-MB-468, Caco-2, A2780, mantle cell lymphoma cell lines and other hematological cell lines) (Alvarez-Berrios et al., 2014; Milani et al., 2009; Saliev et al., 2017). In humans, locoregional hyperthermia has been combined with gefitinib in patients with non-small cell lung cancer, which was feasible in a low number of patients (n = 11) (Qin et al., 2016). In a phase II study, *Gadaleta-Caldarola* et al combined treatment with sorafenib and locoregional hyperthermia in 21 patients with hepatocellular carcinoma. This was feasible, well tolerated and led to partial response in 1 patient and stable disease in 11 patients (median time to progression of 5.2 months (95%-CI 4.2–6.2) (Gadaleta-Caldarola et al., 2014). The combination of cisplatin, lapatinib and locoregional hyperthermia in recurrent cervix carcinoma in previously irradiated area was studied in a phase I trial. Although the combination is of interest due to one observed complete pathological response, of the 8 studied patients only 1 patient was able to complete treatment as planned (mainly due to enhanced cisplatin cytotoxicity), which makes this treatment not feasible (Meerten et al., 2015). Combination of immunotherapy (checkpoint inhibitors) with hyperthermia has been studied less and remains anecdotal. To the authors best knowledge, only one case study using the combination of checkpoint inhibitors (ipilimumab and nivolumab) with hyperthermia (combination of locoregional and WBH) has been reported, resulting in a complete remission in a patient with stage IV triple negative breast cancer with pulmonary metastases (Kleef et al., 2018). As earlier described hyperthermia is known to elicit an antitumor immune response by transference of tumor-antigen to APC by HSP (Toraya-Brown and Fiering, 2014). Furthermore, hyperthermia modulates both innate and adaptive immune responses (Repasky et al., 2013). Heat has several beneficial and non-beneficial effects on cellular immunity, which is of interest in the combination of checkpoint inhibitors and hyperthermia. Overall, hyperthermia in the temperature range of WBH increases the amount of lymphocytes, monocytes and granulocytes and immune cell activity is increased (Frey et al., 2012b).

Therefore, the combination of hyperthermia and immunotherapy is of interest in preclinical studies and clinical case studies, but the possible benefit of these immune mechanisms and possible potentiation of targeted therapy and/or immunotherapy remains speculative until clinical trials have been performed. However, given the earlier mentioned disadvantages of WBH, further clinical studying of this combination is likely to be restricted to locoregional hyperthermia.

5. Conclusion

This review points out that WBH has a potential value when added to chemotherapy, but this remains highly speculative. In several phase II trials, studying a total of 350 evaluable patients, the combination of WBH with chemotherapy did give promising results. In often heavily pretreated patients objective responses were observed in several types of advanced malignancies, albeit at the cost of a high proportion of patients suffering from grade 3 and 4 toxicities attributable to chemotherapy, WBH or the combination. Convincing evidence of the additive value of WBH is thus lacking, in contrast with evidence for local and regional hyperthermia, which has proven additive value to chemotherapy for specific indications. As nowadays, systemic treatment of malignant diseases is an evolving field with an increasing emphasis on targeted therapy and immunotherapy, the disadvantages of WBH (invasiveness, elaborate supportive care, high costs) make this treatment modality far less attractive. This, combined with the lack of follow up (phase III trials) given to the phase II trials, it is unlikely that WBH as adjunct to existing chemotherapy treatments will ever find its way in routine clinical care.

Author's contribution

GL performed the literature search and critical appraisal and drafted the first version of the manuscript. HC and CvH revised the manuscript. All authors are responsible for the final content and approve the final version of the manuscript.

Table 3
Phase II studies combining whole-body hyperthermia with systemic therapy: toxicities and mortality.

Study	Tumor type	Antineoplastic agent(s)	Toxicity (percentage of patients, unless stated otherwise)	Mortality[1]	Cause of death
	Gynaecological cancer				
(Atmaca et al., 2009)	Ovarian cancer	Carboplatin	Grade 3 or 4: leucopenia 49%, thrombocytopenia 65%, anemia 49%, nausea 2%, bacterial infection 11%, mucosal herpes 4%, cardiac 2%	No	n.a.
(Douwes et al., 2004)	Ovarian cancer	Cisplatin or carboplatin, induced hyperglycemia	No grade 4, grade 3: leukopenia 14%, emesis 14%	No	n.a.
(Westermann et al., 2001)	Ovarian cancer	Carboplatin	Grade 3 or 4 (percentage of cycles): leukopenia 32%, thrombocytopenia 50%, anemia 23%, nausea/vomiting 4%. One case of complete bowel obstruction and one case of difficult arousal post-procedure.	No	n.a.
(Richel et al., 2004)	Cervical cancer	Carboplatin	Grade 3 or 4 (percentage of cycles): leukopenia 35%, thrombocytopenia 61%, anemia 22%, nausea 4%, vomiting 4%, fatigue 6%, renal toxicity 2%	No	n.a.
	Gastro-intestinal cancer				
(Hegewisch-Becker et al., 2002)	Colorectal adenocarcinoma	Oxaliplatin + leucovorin + 5-fluoruracil	Grade 4 fatigue syndrome in 6% of cycles combined with WBH (grade 3 in 20%). Other grade 3 (percentage of patients): leukopenia 5%, thrombocytopenia 5%, anemia 5%, nausea/vomiting 5%, mucositis 2%, diarrhea 7%, peripheral neurotoxicity 2%, transient cardiac arrhythmias and signs of myocardial infarction 11%, heart failure 2%	Yes, 1	Sepsis (pneumonia)
(Hildebrandt et al., 2004)	Colorectal adenocarcinoma	5-fluoruracil + folinic acid + mitomycin + induced hyperglycemia + hyperoxemia	In cycles of WBH + CT: grade 4: leukopenia 4%, skin lesions 4%, peripheral nerve damage 8%. Grade 3: leukopenia 16%, thrombocytopenia 28%, anemia 48%, skin lesions 16%, pain 16%, hypotension 12%, dyspnea 44%, hypokalemia 4%, peripheral edema 4%, others 8%.	No	n.a.
(Bakshandeh-Bath et al., 2009)	pancreatic adenocarcinoma	Gemcitabine + carboplatin	Grade 3 or 4: hematological toxicity in 3th and 4th cycle	No	n.a.
	Lung cancer				
(Engelhardt et al., 1982)	Small cell lung carcinoma	Doxorubicin + Cyclophosphamide + vincristine	No complications or side effects (either from WBH or CT)	No	n.a.
(Neumann et al., 1982)	Small cell lung carcinoma	Doxorubicin + cyclophosphamide + vincristine	No severe side effects were observed	No	n.a.
	Sarcoma				
(Bull et al., 1992)	Soft tissue or osteosarcoma	Carmustine	Not graded. Hematological toxicity (most significant thrombocytopenia), non-cardiogenic pulmonary edema, hypotension, sepsis, dermal complications, neuropathy, diarrhea, sinus congestion	No	n.a.
(Westermann et al., 2003)	Soft-tissue sarcoma	Ifosfamide + carboplatin + etoposide	Grade 3 or 4 (percentage of cycles): leukopenia 80%, infection 2%, thrombocytopenia 61%, anemia 15%, gastro-intestinal 1%, nausea/vomiting 2%, hepatic toxicity 1%, renal toxicity 1%	Yes, 2	Sepsis (in both patients associated with urethral obstruction)
(Wiedemann et al., 1996)	Sarcoma	Ifosfamide + carboplatin + etoposide	Grade 3 or 4: thrombocytopenia 58%, leukopenia 100%, anemia 33%, severe renal impairment 8%, ventricular arrhythmias 25%, pressure sores 25%	No	n.a.
	Other cancers				
(Engelhardt et al., 1990)	Melanoma	Cisplatin + doxorubicin	Not graded. No enhancement of chemotherapy toxicity except for a slight enhancement of bone marrow toxicity.	No	n.a.
(Bakhshandeh et al., 2003)	Pleural mesothelioma	Ifosfamide + carboplatin + etoposide	Grade 3 or 4 (percentage of cycles): neutropenia 74%, thrombocytopenia 33%, infection 5%, gastro-intestinal 1%, nausea 9%, vomiting 4%, skin 3%	Yes, 1	Sepsis

Abbreviations: n.a. = not applicable, WBH = whole-body hyperthermia, CT = chemotherapy.
[1] Treatment related mortality.

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None.

Conflict of interest statement

No potential conflicts of interest declared.

Appendix A. Supplementary data

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