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review

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Window-of-opportunity trials to evaluate clinical activity of new molecular entities in oncology

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Background: The introduction of molecular targeted agents (e.g. monoclonal antibodies or kinase inhibitors) and cancer vaccines has raised the question whether alternate clinical trial designs, including window trials, are better suited to evaluate such new molecular entities (NMEs) and improve their approval rates. In window trials, patients receive an NME for a window of time before starting standard treatment allowing the evaluation of an NME in tumors unperturbed by previous therapies.
Methods: A systematic literature search was conducted to identify window trials in adult and pediatric oncology.
Results: Twenty-nine window trials were identified and reviewed, 13 in pediatric and 16 in adult oncology. Most of the trials (20/29) tested cytotoxics known to have activity in other clinical situations. In contrast to trials with pretreated patients, the window trials established the antitumor activity of melphalan, topotecan, epirubicin and etoposide in untreated patients with rhabdomyosarcoma or small-cell lung cancer. In window trials with ineffective or modestly active NMEs, we found no indication of a significant negative effect on overall survival for participating patients.
Conclusions: Provided close safety monitoring and careful patient selection, window trials are a safe option to investigate potential clinical activity of NMEs.
Key words: new molecular entities, safety monitoring, systematic review, window trial

introduction

Despite the high number of new molecular entities (NMEs) in clinical investigation, the success rate of new approved oncology NMEs has not significantly increased. To reduce attrition rate, several approaches have been proposed, including improved clinical trial designs [1–4]. Traditionally, the safety and early efficacy profile of an oncology NME is first assessed in patients who have exhausted standard treatments [5]. This approach was originally developed for cytotoxic NMEs, but non-cytotoxic NMEs may require a different clinical development path. These NMEs often inhibit specific proteins of tumor signaling pathways, tumor microenvironment, or are designed to modify the host immune system (e.g. tumor cancer vaccines). The activity of such NMEs may be obscured by high tumor burden or treatment resistance. Consequently, NMEs can inadvertently be discarded from future development because they are deemed inactive. In the following, we reviewed 'window-of-opportunity' clinical trials, or short window trials, to determine whether this trial design offers a valuable alternative to detect activity of NMEs [6].

In a window trial, the patient agrees to delay standard anticancer therapy to first receive an NME or novel treatment regimen. The aim is to obtain knowledge about antitumor activity of the NME or regimen in a disease state that is not disturbed by previous or simultaneous treatments. Hence, the setting of the window trial is common in early advanced or metastatic disease and the tumor may not be resistant to selective inhibition of a novel cancer target. The end point of the window trial is a clinical end point, such as tumor response or progression-free survival (PFS) at a predefined early time point. The tumor response is often assessed by radiographic imaging. In some instances, such as in leukemia, pathology-based assessments are used (e.g. bone marrow responses).

For the following review, we excluded trials with 'neoadjuvant' or 'induction-regimen' designs. While neoadjuvant or induction-regimen designs include a treatment window, this window is part of a multimodality and sequential treatment concept. By contrast, window trials focus on assessing antitumor activity of a single NME or treatment regimen independently of the follow-on treatment. Neoadjuvant trials are designed to 'help' the subsequent treatment, generally by killing subclinical disease or achieving significant tumor cytoreduction to obtain superior surgical or other curative outcome. Therefore, pathological response assessments in tumor tissue, e.g. colorectal, breast or lung cancer surgical specimen, are more common than clinical end points in such neoadjuvant trials. We also excluded trials evaluating pharmacodynamic end points during a time window

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before surgery in metastatic or advanced disease unless response rate or another antitumor clinical outcome was reported. Examples of studies we excluded are blood flow measurements after antiangiogenic therapy in rectal cancer [7], molecular pathway analyses after anti-folate chemotherapy in breast cancer [8] and epidermal growth factor receptor (EGFR) or human epidermal growth factor receptor 2 (HER2)/neu expression with downstream pathway modulation after EGFR [9] or HER2 [10] inhibition in breast cancer patients. In these trials, patients are treated with an NME for a short period of time to determine whether the agent has the desired pharmacodynamic or molecular effect. These studies are often too short to evaluate clinical end points. Based on the above-outlined definitions, the following review assessed the benefits and risks of window trials to evaluate NMEs in oncology patients.

literature search criteria

Using 31st of August 2010 as a cut-off date, we first searched Medline using the terms 'window trial in cancer' and 'window of opportunity trial in cancer'. We obtained 223 and 24 citations, respectively. However, many of these citations did not fit the definition of a window trial with a clinical end point as described above. The search terms mostly identified biomarker studies that evaluated novel markers to assess prognosis of metastatic disease and surgical or radiotherapeutic interventions for the treatment of cancer. Additional literature searches of oncology journals and scientific meetings using cross-citation links located additional window trials conducted in the past 30 years.

results

We retrieved a total of 29 published window trials, 13 in pediatric and 16 in adult oncology (Table 1). In seven additional publications, the term 'window trial' was used to actually describe a neoadjuvant treatment and hence did not meet our search criteria [39–46]. Clinical primary end points for the window were mostly response rate (27 trials) and PFS was only used in 6 trials. All window trials included patients with advanced or metastatic disease. Pediatric oncology trials mainly tested 'conventional' cytotoxic drugs, previously used in adults. In 8 of the 16 adult oncology trials, cytotoxic drugs were also evaluated. Nine of the window trials were randomized, but the majority had either a single-arm or a sequential/single-arm design (Table 1).

window trials in pediatric oncology

Since the late 1980s, pediatric oncology groups have used window trials to assess novel treatment regimens for treatment-resistant malignancies, such as high-risk rhabdomyosarcoma [47, 48]. The first agent to be evaluated in a window trial was melphalan [12]. When melphalan achieved only one partial response in 13 pretreated children and its clinical pharmacokinetic profile was inconsistent with previous animal studies, melphalan was reevaluated in 13 untreated children for the duration of 6 weeks [12]. Remarkably, 10 of the 13 children showed partial responses indicating that melphalan definitely had antitumor activity in untreated patients. Since this landmark study, window trials evaluated other cytotoxic drugs as single agents or in combination [13–16, 18, 42, 48, 49]. A meta-analysis of >400 rhabdomyosarcoma patients who participated in these window trials suggested that participating children did not suffer from a lower survival outcome [48]. Hence, this trial design continues to be used to investigate novel treatment regimen in metastatic or high-risk rhabdomyosarcoma [17]. Given the importance of this trial design in pediatric disease, investigators agreed on some important guidelines for the conduct of window trials in pediatric oncology [50].

Window trials were also used to assess the activity of NMEs in neuroblastoma patients [18, 19]. The novel platinum derivative iproplatin was found to be active. Also topotecan and a topotecan-based regimen were found to be active [19]. As in rhabdomysarcoma patients, the survival outcome for patients participating in the window trial was not inferior to children treated outside of the window trial [51].

Topotecan was investigated in pediatric patients with osteosarcoma [22], medulloblastoma [20] and high-grade glioma [21]. In one study, individualized dosing of topotecan was developed for children with medulloblastoma [20].

Recently, rituximab was evaluated in pediatric lymphoma (B-cell non-Hodgkin, including Burkitt's lymphoma) during a window of 5 days before starting chemotherapy [23]. Among the 87 assessable patients, there were 41% responders, which was lower than the targeted range of 45%–65%. This was the first assessment of rituximab in children and provided insights into safety and pharmacokinetic in the absence of chemotherapy. Additionally, response data were collected for design of future studies.

window trials in adult malignancies

In contrast to pediatric oncology trials, window trials in adult patients have played a less prominent role, and hence, there is less knowledge on how this trial design may help with the evaluation of NMEs in adults.

breast cancer. In the 1960s and 1970s, breast cancer trials often evaluated single-agent activity of new compounds for one or two cycles before combining them with other agents [52]. While these studies cannot be defined as window trials since a standard treatment was not yet established, nonetheless this approach suggested that sequential chemotherapy had no negative impact for patients enrolled in these early trials. Once a first-line standard treatment was established, two window trials evaluated cisplatin and carboplatin in previously untreated patients [24, 25]. These two studies were relatively small but were able to establish activity of platinum-based treatments. In contrast to these smaller studies, the phase III CALGB 8642 study was the largest window trial and prospectively evaluated the appropriateness of the window trial design in adult cancer patients [26]. Before standard treatment with cyclophosphamide, doxorubicin and fluorouracil (CAF), patients were randomly allocated to five distinct cohorts of cytotoxics. Patients were all treated for up to four cycles during ~12 weeks. The randomization process was designed to limit

Table 1. Summary of window trials in pediatric and adult oncology studies

Tumor type	Evaluated compound in the window	End point	Predefined duration of window (weeks)	Design	Number of patients	Response results	Reference
Pediatric							
Advanced solid tumors	Cyclophosphamide-based regimen	RR	None	Randomized	12	83% (10/12)	Carpenter et al. [11]
Rhabdomyosarcoma	Melphalan	RR	6	Single arm	13	77% (10/13)	Horrowitz et al. [12]
	Topotecan	RR	6	Single arm	48	46%	Pappo et al. [13]
	Ifosfamide/doxorubcin	RR	12	Single arm	152	63%	Sandler et al. [14]
	Vincristine/melphalan	RR	12	Randomized	128	74% (OS at 3 years 55%)	Breitfeld et al. [15]
	Ifosfamide/etoposide					79% (OS at 3 years 27%)	
	Topotecan/cyclophosphamide	RR	6	Single arm	62	47%	Waterhouse et al. [16]
	Irinotecan	RR	6	Sequential single arm	69	42% (PFS 1.21 years)	Pappo et al. [17]
	Vincristin/irinotecan					70% (PFS 1.29 years)	
Neuroblastoma	Ifosfamide	RR	6	Randomized	173	70%	Castleberry et al. [18]
	Epirubicin					26%	
	Carboplatin					77%	
	Iproplatin					67%	
	Paclitaxel	RR	6	Sequential single arm	100	25%	Kretschmar et al. [19]
	Topotecan					67%	
	Cyclophosphamide/topotecan					76%	
Medulloblastoma	Topotecan	RR	6	Single arm	36	47%	Stewart et al. [20]
High-grade glioma	Procarbazine	RR	8	Sequential single arm	14	7% (1/13)	Chintagumpala et al. [21]
	Topotecan					0% (0/14)	
Osteosarcoma	Topotecan	RR	3	Single arm with dose escalation	27		Seibel et al. [22]
B-cell NHL	Rituximab	RR	3–6	Single arm	87	41%	Meinhardt et al. [23]
Adult							
Breast cancer	Cisplatin	RR	18	Single arm	20	47% (9/19)	Sledge et al. [24]
	Carboplatin	RR	3	Single arm	20	20% (4/20)	Kolaric et al. [25]
	Trimetrexate	RR	12	Randomized phase III window drug + CAF	365	60% (OS: 23.1)	Costanza et al. [26]
	Melphalan					41% (OS: 13.2)	
	Amonafide					44% (OS: 22.5)	
	Carboplatin					42% (OS: 14.9)	
	Elsamitrucin					33% (OS: 21.3)	
SCLC	Epirubicin	RR	3–6	Single arm	40	50% (OS: 8.3)	Blackstein et al. [27]
	24-h etoposide infusion	RR	18	Randomized	39	10%	Slevin et al. [28]
	2-h etoposide infusion × 5 days					89%	
	2-h etoposide infusion × 5 days	RR	18	Randomized	94	81% (7.1 months)	Clark et al. [29]
	1-h etoposide infusion × 8 days					87% (9.4 months)	
	VAC versus menogaril	RR	Open	Randomized	86	42% versus 5%	Ettinger et al. [30]
	Imatinib	RR and PFS	3 and 6	Single arm	14	0% (TtP 0.8 months)	Johnson et al. [31]

Table 1. (*Continued*)

Tumor type	Evaluated compound in the window	End point	Predefined duration of window (weeks)	Design	Number of patients	Response results	Reference
NSCLC	Sorafenib	RR and PFS	16	Single arm (weekly monitoring)	25	12% (OS 8.8 months)	Adjei et al. [32]
	CCI-779 (temsirolimus)	RR and PFS	Open	Single arm	55	8% (PFS 2.3 months; OS 6.6 months)	Molina et al. [33]
	Erlotinib followed by gemcitabine + cisplatin (Arm A) versus gemcitabine + cisplatin followed by erlotinib (Arm B)	PFS	Open	Randomized	340	Median OS: 7.7 months for Arm A versus 10.8 months for Arm B	Gridelli et al. [34]
CRC	Enzastaurin	PFS and RR	180	Single arm	27	1.9 months (RR 0%)	Glimelius et al. [35]
	Cetuximab	RR[a]	6	Single arm with dose escalation	62	15%	Tabernero et al. [36]
	Cetuximab	RR	Open	Single arm	39	10%	Pessino et al. [37]
Prostate cancer	Tasquinimod	PFS	NA	Randomized	NA	NA	http://clinicaltrials.gov (Identifier NCT00560482)
ALL	Topotecan	RR	3	Single arm	14	7% (1/14)	Gore et al. [38]

[a]Pharmacodynamics was the primary end point, but RR was recorded.

RR, response rate; OS, overall survival; NHL, non-Hodgkin's lymphoma; CAF, cyclophosphamide, doxorubicin and fluorouracil; SCLC, small-cell lung cancer; VAC, cyclophosphamide, doxorubicin and vincristine; PFS, progression-free survival; TtP, time to progression; NSCLC, non-small-cell lung cancer; CRC, colorectal cancer; NA; not applicable; ALL, acute lymphoblastic leukemia.

patients' accrual to inactive arms. Thus, it took 7 years to include 365 patients. As with pediatric patients, the authors also evaluated the risk of patients not receiving immediate treatment with the approved standard therapy. Patients in the group CAF plus NMEs had a median survival of 17 months, while patients receiving CAF alone had a median survival of 20 months. This difference was not statistically significant ($P = 0.07$). Additional analyses found that poor survival was associated with previous treatments ($P = 0.0028$), lower performance score ($P = 0.0002$) and presence of visceral metastases ($P = 0.01$).

small-cell lung cancer. Similar to the situation in breast cancer, single-agent activity was explored in several early trials before the establishment of combination chemotherapy as reference treatments. Window trials in small-cell lung cancer (SCLC) patients were conducted to improve the treatment regimen with known cytotoxic agents, such as epirubicin [27] and etoposide [28, 29]. The design was justified because patients were later offered combination chemotherapy. Etoposide dosing schedules were investigated in two separate randomized window trials [29]. These trials established the combination of etoposide given over several days as a short infusion and cisplatin as an effective alternative treatment of SCLC. In a fourth window trial, menogaril was inferior to standard vincristine, doxorubicin and cyclophosphamide [30]. While menogaril produced no tumor response in SCLC patients, the 12-month survival rates were 24% compared with 28% in the control group. A similar result was observed in a trial with imatinib [31]. Hence, both these trials [30, 31] with an inactive NME suggested that patients in a window trial are not at a survival disadvantage.

non-small-cell lung cancer. Window trials in patients with metastatic non-small-cell lung cancer (NSCLC) have only recently been implemented. A two-stage Fleming design was used to assess the activity of sorafenib. The study was closed early because the protocol-specified response criterion was not met in the first stage and only 1 of 20 patients showed a tumor response [32]. Participating patients were monitored weekly for progression. In contrast to the pediatric window trials, the window of the administration was not limited to a specific duration, which is perhaps justified for cytostatic agents. Given the mechanism of action of antiangiogenic agents and as indicated by a rate of stable disease of 28% (7/25), PFS may have been a better end point than response rate in this trial. The median overall survival (OS) of 8.8 months was comparable to historic platinum-based doublet front-line treatments [53]. A similar window trial with a two-stage Fleming design was conducted with CCI-779 (temsirolimus) [33]. All the prespecified patients were enrolled. Patients in this trial seemed to have a lower OS (median 6.6 months) compared with the historic median OS of 7.9 months [53]. In the past 3 years, NMEs have changed the standard of front-line treatment and today median OS in trial patients is ~12 months [54, 55]. Hence, the OS of both window trials need to be interpreted in the appropriate historic context, and the median OS of both trials was within the range of historic OS for standard platinum-based doublet regimen. Recent presentations at

scientific meetings and reviews further suggest that more window trials are being planned or implemented in patients with NSCLC [56–58]. However, the TORCH trial in stage IIIb/IV NSCLC may point to the limits of window trials in NSCLC. In this trial, the EGFR inhibitor erlotinib was compared as up-front treatment followed by gemcitabine + cisplatin at time of progression (Arm A) with the same standard chemotherapy followed by erlotinib (Arm B) [34]. Median OS at a protocol-defined interim for 340 patients was significantly inferior in Arm A (7.7 months) compared with Arm B (10.8 months). Once details of the TORCH trial are released, it will be possible to further assess the risks of conducting a window trial in NSCLC patients.

colorectal cancer. While in colorectal cancer (CRC) patients, neoadjuvant trials can be conducted in patients with resectable primary or metastatic tumors [59], window trials in metastatic patients have been comparatively rare. Recently, a window trial in asymptomatic, metastatic CRC patients was carried out [35]. The rationale for designing this trial was based on the experiences from four chemotherapy trials [60–63]. Delaying first-line treatment in asymptomatic patients was investigated in two trials [60, 61]. In the Nordic trial [60], delaying first-line chemotherapy with bio-modulated 5-fluorouracil (5-FU) resulted in shorter OS compared with initiating chemotherapy immediately at the time of diagnosis. In contrast, this was not seen in the Australasian–Canadian trials [61]. In both studies, quality of life was better in patients who received delayed chemotherapy. In the Nordic trial, patients were monitored clinically every second month and therapy in the delayed treatment group was not initiated until manifestation of clinical cancer symptoms. In the AGITG + NCIC trial, patients were monitored clinically every month (radiographic assessment was done every 3 months) and therapy was started upon clinical progression. In addition to these two studies in asymptomatic CRC patients, sequential chemotherapy appears to be as effective as a standard combination therapy. In the UK-MRC FOCUS trial, 2135 patients with previously untreated metastatic CRC were randomly assigned to receive single-agent 5-FU with leucovorin until progressive disease followed by single-agent irinotecan; single-agent 5-FU with leucovorin until progressive disease followed by combination chemotherapy of either oxaliplatin or irinotecan plus 5-FU with leucovorin or combination chemotherapy of either oxaliplatin or irinotecan plus 5-FU with leucovorin [62]. Patients who potentially could have a curative tumor resection if responding to chemotherapy were excluded. No statistically significant difference in OS was observed between the treatment arms. Patients who initially received single-agent therapy had fewer side-effects compared with the combination regimen. Similar results were observed in the Dutch CAIRO study that enrolled 820 patients with metastatic CRC [63]. These four studies suggested that a window trial with a PFS end point of 6 months was justified in asymptomatic CRC patients (patients without symptoms and no adverse clinical signs) to evaluate the activity of enzastaurin, a novel inhibitor of the protein kinase C-beta isoenzyme [64]. Patients who potentially were candidates for chemotherapy-induced curative tumor resection were not eligible. All patients were monitored closely assessing tumor responses by computer tomography and changes in serum lactate dehydrogenase or carcinoembryonic antigen at first, second and then every other month. At first sign of progression based on imaging or clinical symptoms, patients were discontinued from study and were eligible to receive standard chemotherapy. Follow-up survival assessment showed a median OS of 23.5 months [65], which was consistent with historical OS based on meta-analysis of recent first-line metastatic CRC trials [66].

Two additional window trials in CRC patients were conducted with the EGFR inhibitor cetuximab before standard chemotherapy (FOLFIRI, 5-FU, leucovorin, irinotecan with cetuximab) [36, 37]. The response rates of monotherapy cetuximab in these trials (10%–15%) (KRAS mutation status was not reported) are comparable to the 10%–15% response rates in patients relapsing after combination chemotherapy [67, 68].

prostate cancer. In prostate cancer patients, we found only one ongoing window trial with tasquinimod (ABR-215050). The study is being conducted in asymptomatic hormone-refractory metastatic prostate cancer patients who do not yet require first-line chemotherapy with docetaxel and prednisone (http://clinicaltrials.gov/ct2/show/NCT00560482). Similar to the study in asymptomatic CRC patients, disease progression is being evaluated by clinical symptoms combined with sensitive radiographic imaging.

acute lymphocytic leukemia. Finally, a window trial was conducted in high-risk patients with acute lymphocytic leukemia, in which topotecan was evaluated in short windows of 3 or 6 weeks, respectively [38]. Subsequent to this window treatment, all patients were treated with the standard regimen of prednisone, vincristine, daunorubicin and peg-asparaginase. Topotecan was found to have only modest activity.

discussion

With the exception of pediatric oncology, window trials are not commonly used in oncology. In the past, the majority of window trials evaluated 'conventional' or established cytotoxic NMEs. Only recently cytostatic NMEs are being assessed in window trials. Also, statistical methods kept pace with this development were developed and applied to limit patient numbers in window trials without losing the power of estimating a drug effect. By using two-stage designs, in which early response and toxicity are used as independent end points, early decision making is possible to identify active or inactive NMEs [69, 70]. In pediatric oncology, the use of window trials has led to the identification of important cytotoxic treatments, first melphalan and then topoisomerase inhibitor-based regimen for treatment of high-risk rhabdomyosarcoma [12, 48].

The debate on the rationale of conducting window trials often centers on the ethical justification of delaying standard first-line treatment [71–73]. At first glance, evaluating an NME by delaying standard first-line therapy in patients with advanced/metastatic disease appears to be ethically problematic [74]. However, a closer look at the experience of window trials

shows that patients were carefully selected for such trials and thus benefit–risk concerns were addressed. For instance, drugs with a promising cytotoxic profile were evaluated in patients with high-risk disease, such as rhabdomyosarcoma or SCLC [12, 28, 48]. In all instances, the patient population was kept as homogenous as possible to allow a consistent and rapid detection of disease progression. Nonetheless, subgroups were retrospectively identified which should be excluded in future window trials to further minimize the risk of enrolling inappropriate patients. For example, breast cancer patients with visceral disease were found to carry a higher risk for tumor progression even if low disease burden or asymptomatic conditions were present at the start of the trial [26]. Mixing patients who had become refractory to past chemotherapy (>6 months) was also found to unfavorably affect the outcomes. For instance, pediatric patients with rhabdomyosarcoma had different response rates if they had been briefly treated in the past compared with those that were never treated with chemotherapy [73]. In trials where the cancer shows advanced symptoms, a window trial or delaying the standard chemotherapy appears to have detrimental effects. For example, the recent TORCH trial in NSCLC exploring the sequence of administration of erlotinib and combination chemotherapy [34] raises two important questions for future window trials in NSCLC: (i) is PFS a safe end point and (ii) should NSCLC window trials be conducted only in patients with asymptomatic conditions? Trial details have not been published, so it is not possible to determine whether frequent imaging was conducted in this trial as in previous trials [32]. Hence, it is possible that tumor growth was substantial at time of progression and thus became unresponsive to current standard chemotherapy [34]. If despite best imaging assessments patients progressed and were unresponsive to subsequent chemotherapy, window trials should likely only be conducted in a very selected group of patients. As the similar experiences in CRC suggest, window trials may have to be conducted in patients with asymptomatic disease and good performance status. Importantly, retrospective and prospective assessments of OS indicate that patients participating in window trials with ineffective or effective NMEs had similar OS as patients not participating in window trials [26, 30, 32, 33, 48, 51, 65].

In addition to the concern of delaying front-line therapy, there is a theoretical possibility that NMEs may induce resistance to subsequent therapies. However, this concern has not yet been confirmed in the past trials. For instance, the prospective trial CALGB 8642 in breast cancer patients suggests that there was no resistance toward the standard chemotherapy which followed the NMEs. Lastly, the concern that NMEs would add to the toxic effects of the follow-on standard (chemo)therapy has also not been observed in our review. Perhaps, the patient selection for the window trials and the careful monitoring during the window trial reduce the likelihood of exposing patients to unexpected toxic effects.

To further ensure safety of patients participating in window trials, close monitoring plans are generally put in place to detect progression as early as possible. The use of advanced imaging tools (e.g. positron emission tomography) [75, 76], the increased understanding of blood-based markers for assessing progression [77] and the ability to start immediate 'salvage' treatments help with the implementation of window trials. Increasing frequency of standard radiologic examinations during the window period may also offer a way to closely monitor patients participating in window trials, such as weekly [32], bi-weekly [36] or monthly monitoring [78]. Because

Table 2. Points to consider when designing window trials for new molecular entities (NMEs)

Established or favorable safety profile of NME
Ability to closely monitor disease to detect possible progression
Radiographic detection, e.g. high-resolution CT, functional imaging
Blood-based markers associated with disease progression, e.g. tumor markers, LDH
Type of cancer and stage
Window duration
Shortest possible window (e.g. 2–4 cycles depending on cancer and stage) for both cytotoxic and cytostatic NMEs
Delay in therapy has no anticipated negative outcome
For cytotoxic NMEs: known high resistance to established therapies, such as <20% response rate, i.e. no effective standard therapy
For cytostatic NMEs: good performance status patients, no laboratory abnormalities or other conditions indicating prompt need of standard therapy
End point
Cytotoxic NME: response rate
Cytostatic NME: progression-free-survival
Convincing antitumor activity (based on animal or previous clinical studies)
Informed consent should contain the following:
Combined window trial with integrated follow-on therapy
Explanation which part of the treatment plan is the window
Allow the patient elect to participate in the study without being forced to enroll in the window
Disclose alternative treatment options
Describe the risks and benefits of participating in the window trial
Disclose the safeguards to the patients that will allow early detection of progression or lack of response if relevant

CT, computer tomography; LDH, lactate dehydrogenase.

tumor growth delay mediated by cytostatic NMEs takes time and translates best to PFS [79, 80], patients treated with such NMEs will need to be treated for extended period of time in the window. Timing of the monitoring tool is critical and this may limit window trials to only such diseases and stages, in which imaging tools, blood-based markers or other validated measurements of progression are established. This will reduce the bias of timing of such monitoring tools.

The benefits of the window trial have been highlighted by the fact that some NMEs that were inactive in previously treated patients were found to be active in the front-line treatment [12, 29]. In addition to finding active NMEs, the window trial delays chemotherapy and its related toxicity and thus may have another important benefit [61]. This is especially true for NMEs with a favorable toxicity profile. For instance, enzastaurin was chosen for a window trial because it was well tolerated and had few grade 3/4 toxic effects [64, 81].

Although pediatric oncology cooperative groups used the window trial, a recent consensus document about future clinical development in pancreatic cancer supported the investigation of NMEs in windows before standard treatment with gemcitabine [82]. While specifically citing the positive experiences in pediatric drug development, the workshop participants did not recommend including window trials in the final consensus document. Whether commercial sponsors will use the window trial design will depend on the ability to quickly identify inactive from active NMEs, reducing attrition rate and lifting the current rate of approval [1, 83]. While the window trial offers the option to clinically determine active compounds early, the 7-year trial duration of a study such as CALGB 8642 would not entice commercial sponsors to implement such studies. Hence, the sponsor should set up trials with an interim assessment to determine the single-agent activity of an NME, and regulatory authorities would have to agree a first study report, while the entire study is being completed.

When considering a window trial, balancing several benefit and risk factors will ensure not only a scientifically sound design but also the safe participation of a patient in such a trial (Table 2). A safe and tolerable drug may be evaluated for PFS provided patients will be carefully and frequently monitored for progression. Patients with good performance status or conditions that do not require immediate therapy will probably also be good candidates for window trials with a PFS end point. By contrast, an NME with potential cardio-, neuro- or marrow toxicity should not be evaluated in a window design unless a safe time period is prescribed.

In conclusion, window trials did identify active NMEs that otherwise would have been discarded. This overall experience, progress in imaging and monitoring tumor progression in patients, raises the question whether window trials should be more widely applied in early phases of drug development. However, no window trial will replace the importance of well-designed randomized phase II studies to estimate success in phase III studies [84]. Rather, window trials should be considered as an option after the First-Human-Dose study as a proof of concept to better inform future phase II designs. In other instances, they can help define single-agent activity of NMEs in carefully selected patients.

disclosure

The author BG has declared no conflicts of interest. ML has indicated that he is fully employed as physician at Eli Lilly and Company, which owns the molecule enzastaurin, cited in this article.

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