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Research paper

Risks and benefits of anticancer drugs in advanced cancer patients: A systematic review and meta-analysis

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ABSTRACT

Background: Randomized clinical trials (RCTs) of anticancer drugs without active comparators in patients who have exhausted standard of care treatment options are debated. We aimed to quantify the safety and the efficacy of anticancer drugs in advanced cancer patients who have exhausted standard of care treatments from RCTs without active comparators.

Methods: This systematic review and meta-analysis was conducted according to preferred reporting Items for systematic review and Meta-Analyses (PRISMA) guidelines (CRD42021243968). A systematic literature search of English language publications from January 1, 2000, to January 7, 2021, was performed using MEDLINE (PubMed). Eligible trials included all RCTs evaluating anticancer drugs in adult patients with advanced solid tumors with a control arm without any anticancer drug consisting of best supportive care with or without a placebo. RCTs performed in the adjuvant, neoadjuvant or maintenance settings were excluded, as were clinical trials evaluating anticancer drugs in combination with radiotherapy. Two authors (C.M.B. and E.C.) independently reviewed the studies for inclusion. Data from published reports were extracted by investigators, and random-effects meta-analysis was performed to estimate the overall hazard ratios (HRs) of progression-free survival (PFS) and overall survival (OS). Correlations between severe toxicity and efficacy was assessed using R^2 measures.

Findings: Of 3551 studies screened, 128 eligible trials were found involving 47,432 patients. The HRs for PFS and OS were 0·58 [95%CI: 0·53–0·63] and 0·82 [95%CI: 0·78–0·85]. The absolute benefits however were limited with PFS and OS gains of 2·1 and 0·5 months. The absolute excesses in all grade, severe grade III, IV and V (death) adverse events between the two arms were +13·9%, 10·2%, and +0·5%. A weak correlation was measured between the excess of severe toxicity and efficacy (all $R^2 < 0{\cdot}2$).

Interpretation: Anticancer drugs evaluated in RCTs against no active treatment benefited trial participants. Severe toxicity did not significantly correlate with efficacy.

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1. Introduction

The two principal goals of any treatment in oncology are to improve patients' quality of life and/or overall survival (OS). While early stage cancer patients might be cured with local treatments, mainly consisting of surgery and/or radiotherapy, patients with advanced cancer who are not eligible for local treatments in a curative intent represent 40 to 50% of all cancer patients and will usually eventually die from their cancer [1]. Anticancer drugs represent the main therapeutic strategy in this latter setting. Cure of patients with advanced solid tumors is extremely rare, but exceptions exist, including patients with metastatic germline tumors who are often cured with multidrug chemotherapy [2], and a minority of patients who may be cured with immunotherapy such as immune checkpoint inhibitors [3,4]. Molecularly targeted agents given based on the presence of a molecular alteration are usually associated with high response rates, but responses are often limited in time due to the occurrence of resistance mechanisms [5,6]. In this context, the potential benefits of anticancer treatments have to be weighed against their potential harm when given to patients with advanced cancer.

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Research in context

Evidence before this study

Randomized clinical trials of anticancer drugs without active comparators in patients who have exhausted standard of care treatments are debated. Beyond single randomized clinical trials, the safety and the efficacy of anticancer drugs in these patients from randomized clinical trials without active comparators were never quantified.

Added value of this study

In this systematic review and meta-analysis, we show that advanced cancer patients who have exhausted standard of care treatments and participate in a randomized clinical trial with a control arm without any anticancer drug overall benefited from the experimental treatment when randomized into the experimental arms with a 42% decrease in the risk of disease progression and a 18% decrease in the risk of death. The benefits however were limited with progression-free survival and overall survival gains of 2·1 and 0·5 months. The absolute excesses in all grade, grade III, IV and V adverse events between the arms were +13·9%, 10·2%, and +0·5%, and a weak correlation was measured between efficacy and excess in severe toxicity (all $R^2 < 0{\cdot}2$).

Implications of all the available evidence

Overall, randomized clinical trials versus no active treatment advanced cancer patients remain ethical and attractive. Contrary to a common perception, efficacy does not correlate with safety. Adverse events reported in our meta-analysis constitute a basis for discussion with advanced cancer patients in view of the potential benefits.

In oncology, randomized clinical trials represent the gold-standard approach to evaluate the benefits and risks of a new treatment over standard of care. The risks and benefits of anticancer drugs can be precisely evaluated from the subgroup of randomized trials with control arms that do not contain any anticancer drugs. These trials are proposed to patients when they have exhausted standard of care treatment options. However, the randomization versus no active treatment is increasingly challenging in those patients who are often reluctant to possibly receive best supportive care only [7,8].

We aimed at quantifying the safety and the efficacy of anticancer drugs in advanced cancer patients who had exhausted standard of care treatments by performing a meta-analysis of randomized clinical trials with a control arm consisting of best supportive care with or without a placebo.

2. Methods

2.1. Search strategy and selection criteria

The study protocol is registered in the International Prospective Register of Systematic Reviews (CRD42021243968). Eligible trials for our meta-analysis included all randomized clinical trials evaluating anticancer drugs in adult patients with advanced solid tumors with a control arm without any anticancer drug consisting of best supportive care [BSC] with or without a placebo. Clinical trials performed in the adjuvant, neoadjuvant or maintenance settings were excluded, as were clinical trials evaluating anticancer drugs in combination with radiotherapy. This systematic review was conducted according to preferred reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [9].

To retrieve these trials, a MEDLINE search was performed from January 1, 2000 to January 7, 2021 using the following search terms: "placebo OR best supportive care AND cancer AND controlled randomized trial AND survival". The NIH U.S National Library of Medicine was also searched through clinicaltrials.gov using the keywords “placebo controlled” OR “best supportive care controlled”, “completed”, “terminated studies”, “interventional studies”, “advanced cancer”, “phase 2, 3″ in order to identify missing trials. Abstracts of references that appeared potentially eligible for inclusion were examined independently by two reviewers (C.M.B. and E.C.) and, if deemed relevant, full-text articles including supplementary materials were retrieved and included if appropriate. Disagreements between the two reviewers were resolved by consensus with one of us (C.L.T.). Only papers published in the English language were considered.

2.2. Data analysis

Trial characteristics included tumor type, line of therapy, type of anticancer drug evaluated in the experimental arm, mode of administration, the type of control, phase of the clinical trial, number of patients in each arm, year of publication, type of sponsor, and crossover permission. Efficacy outcome data included overall response rates (ORR), criteria used to assess efficacy, overall survival (OS), progression-free survival (PFS) (or time to progression [TTP] when PFS was not reported), and hazard ratios (HR) for survival outcomes. Safety data included all-grade, grade III, IV and V (death) adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events guidelines used by the authors. Since adverse events related to study drugs were infrequently reported in the trials, we only reported emerging adverse events. When one information was missing in a trial, the population of that trial was not taken into account in the denominator.

The ORR was the proportion of patients with a complete or a partial response in randomized patients. OS was defined as the time from randomization to death whatever the cause. PFS was defined as the time to first progression or death whatever the cause. HRs evaluate the hazard of an event in the experimental arm versus the hazard in the control group, and their associated significance values (p-values). If the HR was not available, it was reconstructed from median survivals and p-values [10]. Proportions of adverse events were calculated by dividing the total number of patients having experienced the adverse event with the total number of patients.

The effect of treatment on OS and PFS was quantified by using the HR without adjusting for any covariate. The effect of treatment on safety was quantified by calculating the difference in rates of adverse events between the treatment arms. Studies with missing HR for a given endpoint were excluded for this particular analysis. Randomized clinical trials tested various treatments in various patient populations. Therefore heterogeneity in treatment effects is expected around the mean effect. A random-effect meta-analysis model using the inverse variance method was selected for pooling due to the anticipated heterogeneity in effects of the various treatments; contrary to fixed effect models, the treatment effect is allowed to vary beyond mere random fluctuations. Treatment effect was assumed to vary according to a Normal distribution around the mean effect. Heterogeneity across studies was estimated from the DerSimonian-Laird estimator and quantified using I^2 statistics. Subgroups were compared with Chisq statistics. Forest plots were used to display HRs and risk differences within individual trials and overall. Means of the time-to-event endpoints weighted on the number of patients of each trial were calculated. Analyses of subgroups of trials included the period of time defined by the publication date in five years intervals, the type of control, and the type of anticancer drug in the experimental arm. P values for the heterogeneity tests are provided. As a

sensitivity analysis, we recomputed the pooled HRs after the exclusion of the trials in cancer types for which the median PFS in the control groups were greater than the highest quintiles, i.e. desmoid tumors, neuroendocrine tumors, thyroid cancers, and prostate cancers.

At the trial level, the linear correlations between the efficacy endpoints (ORR difference, HRs for PFS and OS), and the difference in rates of adverse events were explored with the R^2 measures.

Systematic publication bias was explored using funnel plots of the trial mean differences for asymmetry, and tested using the Egger's test.

All analyses were performed in R v3.6.1 with the meta package.

2.3. Ethic statement

According to the manuscripts of the trials included in our meta-analysis, all patients signed a consent form for trial participation.

2.4. Role of the funding source

There was no funding source for this study.

3. Results

We retrieved 128 trials published between January 1, 2000 and January 7, 2021 that matched our selection criteria (Fig. 1 & Supplementary Table S1). A total of 47,432 patients were included in these trials, including 29,028 patients (61·2%) who received an active anticancer drug, 15,990 (33·7%) a placebo without any active anticancer drug in 102 trials (79·7%), and 2414 (5·1%) BSC only in 26 trials (20·3%) (Table 1). The risk of bias was low for all studies as they were randomized, often placebo controlled and evaluated OS with adequate cut-off date that is not prone to reporting bias. In 47 trials, progression was assessed by an independent committee leading to a very low risk of bias. In the 65 trials with investigator assessed progression, we did not detect bias.

Most of trials were industry-sponsored (82·8%), and published during the 2010–2020 period (70·3%). A cross-over to the experimental arm at disease progression was allowed in 24 trials (18·8%). Most patients were treated in a phase 3 clinical trial (69·5%), and beyond the first line (78·9%). The experimental treatment was a molecularly targeted agent in 75 trials (58·6%), chemotherapy in 19 trials (14·8%), hormone therapy in 14 trials (10·9%), and immunotherapy in 20 trials (15·6%). Mode of administration of the anticancer drug was oral in 83 trials (64·8%), intravenous in 31 trials (24·2%), and intramuscular or subcutaneous in seven trials (5·5%) each. Most frequent tumor types were hepatocellular carcinoma, non-small cell lung cancer, prostate adenocarcinoma and colorectal cancer. None of these tumor types exceeded 20% of the trials. Criteria used to assess the treatment efficacy was RECIST in most trials (78·9%) [11].

The use of a placebo increased over time (84·4% during the last decade versus 68·4% during the first decade) (Table 1). More trials were performed beyond the first line during the last decade (88·9% versus 55·3%) (Supplementary Table S2). The diversity in terms of tumor types increased over time (17 different tumor types during the last decade versus 11 during the first decade).

The primary endpoint of the trials was OS in 71 trials (54%), PFS in 39 trials (30%), TTP in 7 trials (5%), and ORR, disease stabilization rate, PSA decrease, and quality of life in one trial (1%) each. In the seven remaining trials (5%), OS and PFS were co-primary endpoints. Among the 78 trials with OS as a (co)primary endpoint, 39 trials (50%) were statistically positive at the 5% level. Among the 53 trials with PFS or TTP as a (co)primary endpoint, 41 trials (77%) were statistically positive at the 5% level.

The overall HR for PFS was 0·58 [95%CI (confidence interval): 0·53–0·63] (Fig. 2A–C). Average median PFS in the experimental arms was 5·7 months, as compared to 3·6 months in the control arms. The HR improved over time, from 0·87 [95%CI: 0·62–1·23] during the 2000–2005 period to 0·69 [95%CI: 0·61–0·79] during the 2005–2010 period, 0·54 [95%CI: 0·48–0·62] during the 2010–2015 period, and 0·52 [95%CI: 0·46–0·59] during the 2015–2020 period ($P < 0·01$) (Fig. 2A). The HR did not differ significantly between trials using a placebo versus trials with BSC only ($P = 0·58$) (Fig. 2B). Some statistically significant heterogeneity was observed between treatment classes, with HRs that were less favorable with immunotherapy and hormone therapy (0·75 [95%CI: 0·63–0·88]), as compared to chemotherapy (0·53 [95%CI: 0·43–0·65]) and molecularly targeted agents (0·54 [95%CI: 0·49–0·60]) ($P < 0·01$) (Fig. 2C).

The overall HR for OS was 0·82 [95%CI: 0·78–0·85] (Fig. 3A–C). Average median OS in the experimental arms was 11·6 months, as compared to 11·1 months in the control arms. The HR for OS did not

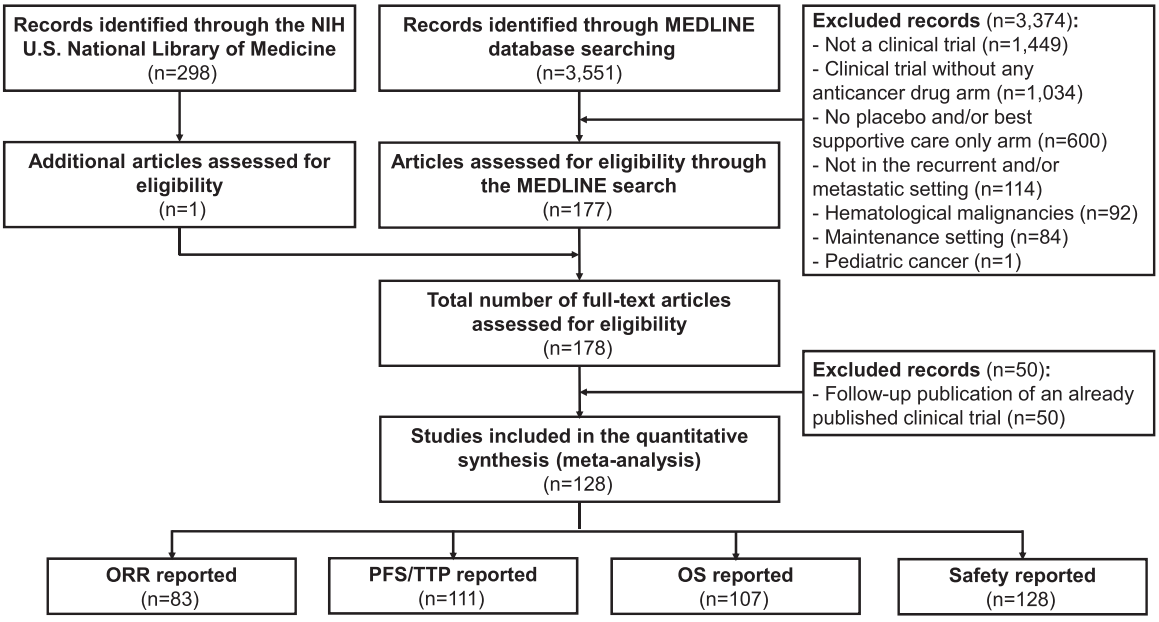

Fig. 1. Study selection process of randomized clinical trials with a control arm without an active drug. ORR = overall response rate; PFS = progression-free survival; TTP = time to treatment progression; OS = overall survival.

Table 1
Characteristics of the trials.

	Trials versus placebo	Trials versus BSC	All trials
No. of trials	102	26	128
No. of patients:	42,037	5395	47,432
- Experimental arm	26,047 (62·0%)	2981 (55·3%)	29,028 (61·2%)
- No active treatment arm	15,990 (38·0%)	2414 (44·7%)	18,404 (38·8%)
Sponsor:			
- Academic	12 (11·8%)	10 (38·5%)	22 (17·2%)
- Industrial	90 (88·2%)	16 (61·5%)	106 (82·8%)
Year of publication:			
- 2000–2009	26 (25·5%)	12 (46·2%)	38 (29·7%)
- 2010–2020	76 (74·5%)	14 (53·8%)	90 (70·3%)
Cross-over allowed	21 (20·6%)	3 (11·5%)	24 (18·8%)
Line of treatment:			
- 1st line	23 (22·5%)	4 (15·4%)	27 (21·1%)
- ≥ 2nd line	79 (77·5%)	22 (84·6%)	101 (78·9%)
Clinical phase of the trial:			
- Phase 2	30 (29·4%)	9 (34·6%)	39 (30·5%)
- Phase 3	72 (70·6%)	17 (65·4%)	89 (69·5%)
Criteria used for efficacy assessment:			
- RECIST	86 (84·3%)	15 (57·7%)	101 (78·9%)
- WHO criteria	8 (7·8%)	7 (26·9%)	15 (11·7%)
- Other	2 (2·0%)	1 (3·8%)	3 (2·3%)
- Not specified	6 (5·9%)	3 (11·5%)	9 (7·0%)
Experimental treatment type:			
- Chemotherapy	6 (5·9%)	13 (50·0%)	19 (14·8%)
- Hormone therapy	13 (12·7%)	1 (3·8%)	14 (10·9%)
- Molecularly targeted agent	68 (66·7%)	7 (26·9%)	75 (58·6%)
- Immunotherapy	15 (14·7%)	5 (19·2%)	20 (15·6%)
Mode of administration:			
- Intravenous	12 (11·8%)	19 (73·1%)	31 (24·2%)
- Oral	80 (78·4%)	3 (11·5%)	83 (64·8%)
- Intramuscular	6 (5·9%)	1 (3·8%)	7 (5·5%)
- Subcutaneous	4 (3·9%)	3 (11·5%)	7 (5·5%)
Tumor type:			
- Hepatocellular carcinoma	22 (21·6%)	2 (7·7%)	24 (18·8%)
- Non-small cell lung cancer	15 (14·7%)	5 (19·2%)	20 (15·6%)
- Prostate adenocarcinoma	17 (16·7%)	0	17 (13·3%)
- Colorectal cancer	10 (9·8%)	4 (15·4%)	14 (10·9%)
- Gastric cancer	6 (5·9%)	3 (11·5%)	9 (7·0%)
- Neuroendocrine tumor	7 (6·9%)	0	7 (5·5%)
- Pancreatic adenocarcinoma	2 (2·0%)	3 (11·5%)	5 (3·9%)
- Renal cell carcinoma	5 (4·9%)	0	5 (3·9%)
- Thyroid cancer	5 (4·9%)	0	5 (3·9%)
- Mesothelioma	2 (2·0%)	3 (11·5%)	5 (3·9%)
- Gastro-intestinal stromal carcinoma	4 (3·9%)	1 (3·8%)	5 (3·9%)
- Sarcoma	3 (2·9%)	1 (3·8%)	4 (3·1%)
- Urothelial cancer	0	2 (7·7%)	2 (1·6%)
- Biliary cancer	2 (2·0%)	0	2 (1·6%)
- Head and neck squamous cell carcinoma	0	1 (3·8%)	1 (0·8%)
- Small cell lung cancer	0	1 (3·8%)	1 (0·8%)
- Melanoma	1 (1·0%)	0	1 (0·8%)
- Glioblastoma	1 (1·0%)	0	1 (0·8%)
Overall response rate:			
- Experimental arm	6·7% (1087/16,260)	9·7% (214/2200)	7·0% (1301/18,460)
- No active treatment arm	1·2% (117/9367)	0·7% (13/1810)	1·2% (130/11,177)

BSC: Best supportive care.
% are the proportions of the total population.

improve over time (P = 0·49) (Fig. 3A). It did not statistically differ between trials using a placebo (0·78 [95%CI: 0·73–0·84]) versus trials with BSC only (0·85 [95%CI: 0·80–0·91]) (P = 0·06) (Fig. 3B). Finally, variations of treatment effect across classes of agents were non-statistically significant with immunotherapy and hormone therapy (0·88 [95%CI: 0·78–0·98]), as compared to chemotherapy (0·76 [95%CI: 0·68–0·84]) and molecularly targeted agents (0·81 [95%CI: 0·77–0·86]) (P = 0·18) (Fig. 3C).

The sensitivity analysis led to the same results. After the exclusion of the 29 trials involving the four tumor types with the longest PFS in the control groups, the pooled HR for PFS was 0·58 and the pooled HR for OS was 0·82, suggesting that the relative treatment effects were similar in tumor types with a slower natural history as compared to tumor types with a more rapid natural history.

The ORR was 7·0% in the experimental arms, and 1·2% in the control arms (Table 1). ORR were the highest in the experimental arms of thyroid cancer (36·7%) and renal cell carcinoma patients (15·8%) trials (Supplementary Table S3). The highest ORR in the control arms was reported in melanoma trials (5·8%).

The proportions of patients experiencing any grade adverse event and grade III, IV adverse events were reported in most of trials, whereas grade V adverse events (death) were reported in around half of trials (Table 2). Absolute excesses of 13·9, 10·2 and 0·5% were observed in the experimental arms as compared to the control arms for all grade, grade III, IV, and V adverse events, respectively. Hormone therapy appeared to be the least toxic class of anticancer drugs, with minimal differences between the experimental and control arms (Table 2). Reporting of adverse events increased over time, with

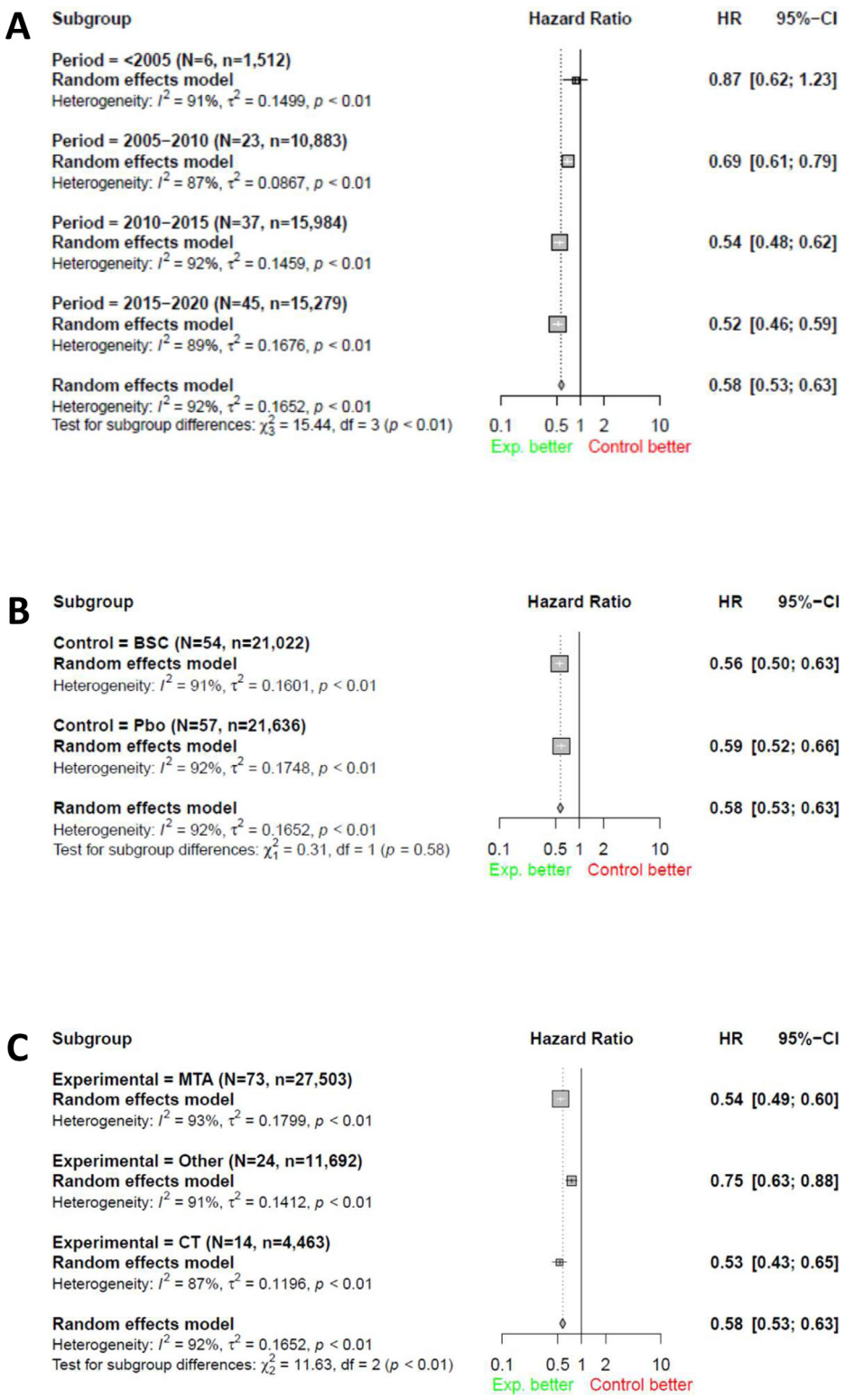

Fig. 2. Forrest plots of progression-free survival according to the treatment period (A), the type of control arm (B), and the type of experimental treatment (C). N represents the total number of studies included in the subgroup, and n the total number of patients. I^2 denotes the quantity of heterogeneity (between 0 and 100%). τ^2 is the inter-study variance. p is the p-value of the heterogeneity test. BSC = best supportive care; Pbo = placebo; HR = hazard ratio; 95%-CI = 95% confidence interval; CT = chemotherapy; MTA = molecularly targeted agent; Other = immunotherapy or hormone therapy; Exp = experimental arm.

higher proportions of patients experiencing adverse events in both experimental and control arms.

At the trial level, a weak correlation was found between the difference in rates of grade III-IV adverse events and efficacy, neither in terms of HR for PFS (R^2 = 0·17) nor in terms of ORR (R^2 = 0·12) and OS (R^2 = 0·003) (Supplementary Figs. S1−S3).

Funnel plots and the Egger's tests indicate that there is no clear publication bias in the direction of the treatment effects for PFS

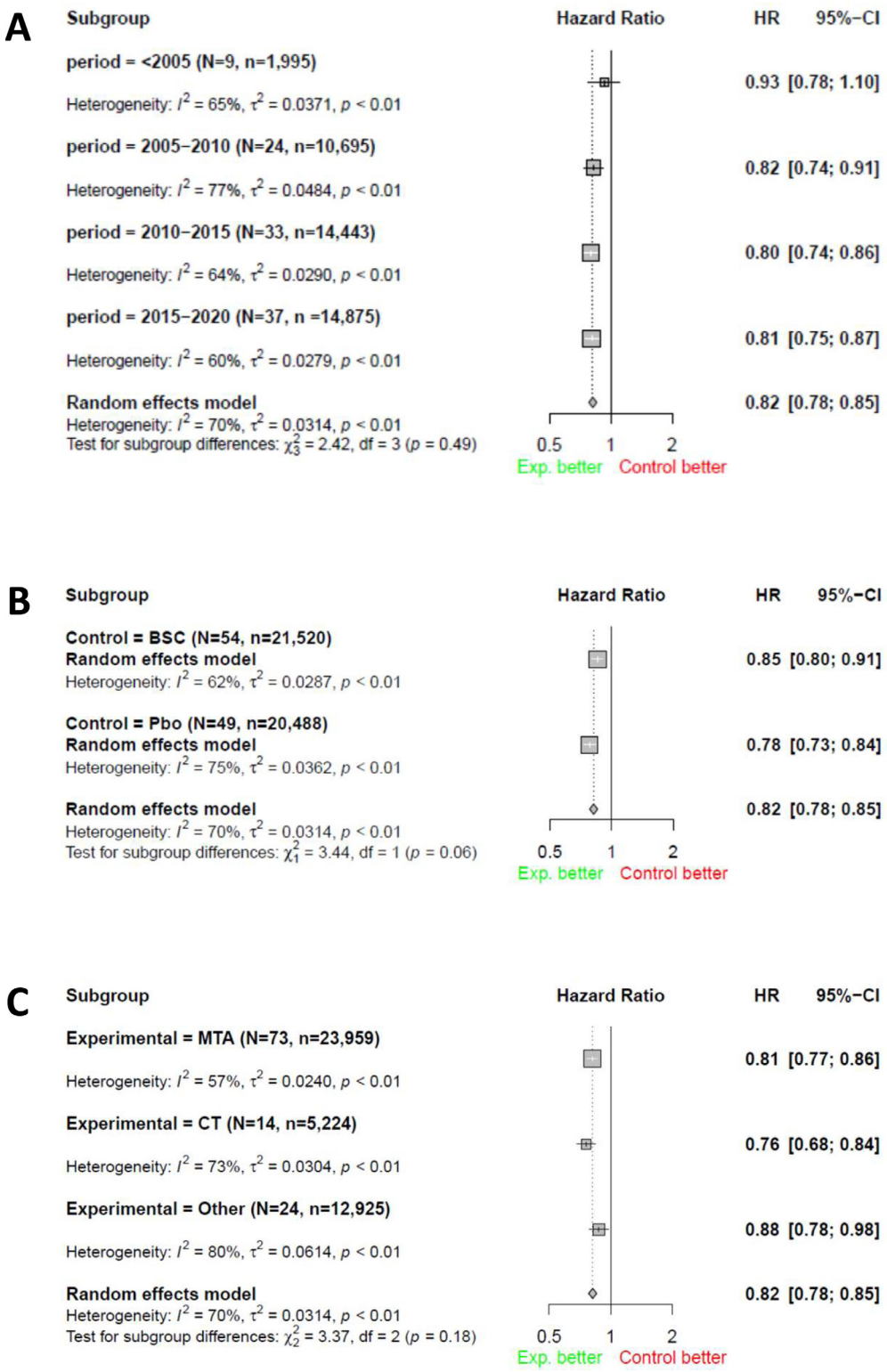

Fig. 3. Forrest plots of overall survival according to the treatment period (A), the type of control arm (B), and the type of experimental treatment (C). N represents the total number of studies included in the subgroup, and n the total number of patients. I^2 denotes the quantity of heterogeneity (between 0 and 100%). τ^2 is the inter-study variance. p is the p-value of the heterogeneity test.. BSC = best supportive care; Pbo = placebo; HR = hazard ratio; 95%-CI = 95% confidence interval; CT = chemotherapy; MTA = molecularly targeted agent; Other = immunotherapy or hormone therapy; Exp = experimental arm.

(P = 0·07), since point estimates appear equally distributed on either sides of the mean effect, but some asymmetry toward stronger effects in small studies for OS (P = 0·002) (Figs. S4, S5). Due to the various investigated treatments, the treatments effect is not expected to be strictly proportional to the effect size and to belong to the triangle.

4. Discussion

Our meta-analysis showed that patients with advanced cancers who have exhausted standard of care and were treated in the experimental arms of randomized trials with a control arm without an

Table 2
Reporting of all emerging adverse events in patients included in oncology randomized clinical trials versus no active treatment according to trial characteristics.

	Experimental arm			No active treatment arm		
	Grade III, IV	Grade V	All	Grade III, IV	Grade V	All
All trials	33·5% (117 trials)	7·8% (67 trials)	77·0% (113 trials)	23·3% (113 trials)	7·3% (58 trials)	63·1% (111 trials)
Type of control arm:						
- Placebo	32·8%	8·0%	76·7%	23·0%	7·6%	64·6%
- Best supportive care	40·8%	4·5%	80·4%	26·2%	3·9%	51·1%
Experimental treatment type:						
- Chemotherapy	41·4%	2·1%	85·4%	21·9%	0·4%	61·8%
- Hormone therapy	33·5%	5·9%	70·4%	32·5%	5·3%	69·6%
- Molecular targeted agent	30·5%	6·6%	73·5%	19·5%	6·7%	57·5%
- Immunotherapy	40·0%	16·4%	91·5%	31·1%	15·2%	83·9%
Year of publication:						
- 2000–2009	23·0%	3·5%	68·0%	17·6%	3·9%	52·4%
- 2010–2020	37·5%	8·5%	80·3%	25·9%	8·0%	67·8%

% are the proportions of adverse events calculated by dividing the total number of patients having experienced the adverse event with the total number of patients.

active anticancer drugs overall benefited from the treatment with a 42% decrease in the risk of disease progression and a 18% decrease in the risk of death. Benefits improved over the last two decades. The excess risks of all grade adverse events, severe adverse events and death, were reasonable. These trials remain therefore attractive and ethical. At the trial level, a weak correlation was found between the efficacy and the rates of severe adverse events.

For obvious ethical reasons, randomized controlled clinical trials with a control arm without an active treatment are performed in advanced cancer patients, when standard treatment options have been exhausted. These trials have become more frequent in the last decade. Most trials in our meta-analysis indeed investigated treatments beyond the first line, especially during the last decade. This can be easily explained by successive implementations of novel first line standard of care treatment options in multiple tumor types. Interestingly, we observed a diversification of tumor types in which novel anticancer drugs were evaluated. These trials were also most often sponsored by industry. This latter trend has been observed in all oncology drug development [12].

Unbalanced randomization is often used to increase the likelihood to receive the experimental treatment, which was the case for almost two thirds of patients included in our meta-analysis. This also reflects that investigators might have had some concerns with the equipoise in this setting. A placebo was used in a large majority of trials, as opposed to BSC only, allowing to minimize the risk of assessments bias. The use of a placebo was more frequent during the last decade. Cross-over was unfrequently implemented in our series, and even less over the last decade. This might be due to the fact that regulatory agencies recently more frequently required the demonstration of an OS benefit for market access [13]. Allowing cross-over might dilute the OS treatment effect, although more appealing for patients participation.

The benefit observed in PFS in our meta-analysis is high according to the European Society of Medical Oncology magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS) [14], but low according to the American Society of Clinical Oncology value framework (ASCO-VF) that also takes toxicity into account for the overall evaluation of the value of a new drug [15]. The relative PFS benefit largely improved over the two decades. This might be related to the more stringent benefit requirements by the regulatory agencies for market access [13]. The OS benefit we report is low according to the ESMO-MCBS and the ASCO-VF [14,15]. The OS benefit did not statistically improve over the two decades. These observations might be reassuring for patients participating in randomized trials against no active treatment beyond standard of care.

An ORR of 1·2% was reported among patients randomized into the control arms without an active drug, which is in line with a previously published meta-analysis [16]. This observation might be due to (1) Spontaneous cancer regressions that might occur, usually following an infection [17], (2) The removal of the primary tumor like in metastatic renal cell carcinoma [18], (3) The delayed anticancer activity of a prior line of treatment [19,20]. Or (4) Tumor assessment errors [21].

We recorded all adverse events reported in the trials independent of their relationship to study treatment. The difference in adverse events frequency between patients treated with an experimental anticancer drug and patients who did not receive an active drug provided a unique opportunity to estimate the proportion of adverse events that are likely imputable to the experimental treatments. The absolute excesses of adverse events between the experimental and the control arms were reasonable. The rates of toxic death and severe adverse events are in line with what we had reported from a review of 51 randomized controlled trials with a similar control arm without an active drug but for which treatment-related adverse events were recorded [22]. Interestingly, all types of adverse events were more frequent during the last decade as compared to the first decade in both the experimental and control arms. This observation may rely in recommendations to more stringently report adverse events [23–25].

We found a weak correlation between the efficacy and the safety at the trial level, which is line with a previous report on drugs approved by the Food and Drug Administration [26], but not with another review that correlated all grade adverse events [27]. The assumption of a correlation between toxicity and efficacy was clearly true for chemotherapy, but less for molecularly targeted agents, hormone therapy and immunotherapy that were evaluated in most of the trials included in our meta-analysis.

One strength of our meta-analysis in the sole inclusion of randomized clinical trials with control arms without any anticancer drug, allowing to minimize biases, and to strictly evaluate the benefits and risks of the anticancer drugs explored in the experimental arms.

Our study has, however, some limitations, the first one being that we had no individual patient data, which strongly limited the exploration of correlations and increased the risk of reporting biases. For the efficacy assessment, TTP had to be used as a proxy for PFS for five trials. For the safety assessment, only the worst grade adverse events were taken into account, ignoring lower grade adverse events that might have occurred in a same patient. In addition, no distinction was made between symptomatic adverse events and biological adverse events that might not translate into symptoms. Moreover, the reporting of adverse events across trials carried out over 20 years was heterogeneous. Another limitation of our study relates to the trials population included. Due to the intrinsic heterogeneity of the data in terms of tumor types and drugs, individual recommendations can hardly be made. In addition, an increasing number of drugs were recently approved based on single-arm trials results, especially in molecularly-defined subgroups of patients, and are not included in this meta-analysis. Finally, we cannot exclude a publication bias in our meta-analysis, as illustrated by a significant asymmetry in the OS funnel plot that might indicate a risk of publication bias of small studies displaying

strong treatment effects on OS. Our results can therefore not be extrapolated to the set of anticancer drugs developed in oncology.

In conclusion, our meta-analysis shows that advanced cancer patients who have exhausted standard of care treatment and participate in a randomized clinical trial with a control arm without any anticancer drug overall benefited from the experimental treatment when randomized into the experimental arms with a 42% decrease in the risk of disease progression and a 18% decrease in the risk of death. The benefits were limited with PFS and OS gains of 2·1 and 0·5 months. While OS gains are well perceived by patients, gains in PFS are often misunderstood [28,29]. Adverse events reported in our meta-analysis constitute a basis for discussion with advanced cancer patients in view of the potential benefits. Overall, randomized clinical trials versus no active treatment in this indication remain ethical and attractive.

Contributors section

C.L.T. and X.P. designed the study. C.M.B, E.C. and C.L.T. searched the literature and collected the data. C.L.T. and X.P. were responsible for accessing, viewing and responsible for the integrity of any datasets used. All authors participated to the interpretation of the data and writing of the paper.

Data sharing statement

The study protocol is registered in the International Prospective Register of Systematic Reviews (CRD42021243968). Raw data are available upon request.

Declaration of Competing Interest

Dr. Moreau Bachelard has nothing to disclose. Dr. Coquan has nothing to disclose. Dr. du Rusquec has nothing to disclose. Dr. Paoletti has nothing to disclose. Dr. Le Tourneau has nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101130.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33.
[2] Loehrer Sr PJ, Gonin R, Nichols CR, Weathers T, Einhorn LH. Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. J Clin Oncol 1998;16:2500–4.
[3] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. New Engl J Med 2019;381:1535–46.
[4] Antonia SJ, Borghaei H, Ramalingam SS, et al. Four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer: a pooled analysis. Lancet Oncol 2019;20:1395–408.
[5] Gainor JF, Dardaei L, Yoda S, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. Cancer Discov 2016;6:1118–33.
[6] Cocco E, Schram AM, Kulick A, et al. Resistance to TRK inhibition mediated by convergent MAPK pathway activation. Nat Med 2019;25:1422–7.
[7] Gerstein HC, McMurray J, Holman RR. Real-world studies no substitute for RCTs in establishing efficacy. Lancet 2019;393:210–1.
[8] Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. N Engl J Med 2020;382:674–8.
[9] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.
[10] Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815–34.
[11] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[12] Booth CM, Cescon DW, Wang L, Tannock IF, Krzyzanowska MK. Evolution of the randomized controlled trial in oncology over three decades. J Clin Oncol 2008;26:5458–64.
[13] Davis C, Naci H, Gurpinar E, et al. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European medicines agency: retrospective cohort study of drug approvals 2009-13. BMJ 2017;359:j4530.
[14] Cherny NI, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefit scale version 1.1. Ann Oncol 2017;28:2340–66.
[15] Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American society of clinical oncology value framework: revisions and reflections in response to comments received. J Clin Oncol 2016;34:2925–34.
[16] Ghatalia P, Morgan CJ, Sonpavde G. Meta-analysis of regression of advanced solid tumors in patients receiving placebo or no anti-cancer therapy in prospective trials. Crit Rev Oncol Hematol 2016;98:122–36.
[17] Challis GB, Stam HJ. The spontaneous regression of cancer. a review of cases from 1900 to 1987. Acta Oncol 1990;29:545–50.
[18] Janiszewska AD, Poletajew S, Wasiutyński A. Spontaneous regression of renal cell carcinoma. Contemp Oncol (Pozn) 2013;17:123–7.
[19] Borcoman E, Kanjanapan Y, Champiat S, et al. Novel patterns of response under immunotherapy. Ann Oncol 2019;30:385–96.
[20] Long GV, Weber JS, Larkin J, et al. Nivolumab for patients with advanced melanoma treated beyond progression: analysis of 2 phase 3 clinical trials. JAMA Oncol 2017;3:1511–9.
[21] Schwartz LH, Mazumdar M, Brown W, et al. Variability in response assessment in solid tumors: effect of number of lesions chosen for measurement. Clin Cancer Res 2003;9:4318–23.
[22] Moreau-Bachelard C, Coquan E, Le Tourneau C. Imputability of adverse events to anticancer drugs. N Engl J Med 2019;380:1873–4.
[23] Moher D, Schulz KF, Altman D, CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987–91.
[24] Djulbegovic B, Clarke M. Ethical issues in the reporting of clinical trials. JAMA 2001;286:1577–8.
[25] Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. JAMA 2013;309:814–22.
[26] Niraula S, Seruga B, Ocana A, et al. The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. J Clin Oncol 2012;30:3012–9.
[27] Abola MV, Prasad V, Jena AB. Association between treatment toxicity and outcomes in oncology clinical trials. Ann Oncol 2014;25:2284–9.
[28] Fallowfield LJ, Catt SL, May SF, et al. Therapeutic aims of drugs offering only progression-free survival are misunderstood by patients, and oncologists may be overly optimistic about likely benefits. Support Care Cancer 2017;25:237–44.
[29] Jenkins V, Farewell V, May S, et al. Do drugs offering only PFS maintain quality of life sufficiently from a patient's perspective? Results from AVALPROFS (assessing the 'VALue' to patients of PROgression free survival) study. Support Care Cancer 2018;26:3941–9.