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Meta-analysis of regression of advanced solid tumors in patients receiving placebo or no anti-cancer therapy in prospective trials

Pooja Ghatalia[a,1], Charity J. Morgan[b,1], Guru Sonpavde[c,*]

[a] Department of Internal Medicine, University of Alabama at Birmingham (UAB), AL, United States
[b] Department of Biostatistics, UAB School of Medicine, United States
[c] Department of Internal Medicine, Section of Medical Oncology, UAB Medical Center, United States

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ABSTRACT

Background: A meta-analysis of prospective trials systematically investigated regression of advanced solid tumors in patients receiving placebo or no anticancer therapy to inform on spontaneous regressions.
Patient and methods: Arms of randomized controlled trials (RCTs) of metastatic solid tumors receiving placebo or no anti-cancer therapy were used. Statistical analyses were conducted to calculate the overall response rate (ORR) and to detect differentials based on histology, progression at baseline and prior therapies.
Results: A total of 7676 patients were evaluable from 61 RCTs evaluating 18 solid tumors. The ORR was 1.95% (95% CI: 1.52–2.48%). There was no significant effect of histology ($p = 0.110$), baseline progressive disease ($p > 0.20$) or the line of therapy ($p > 0.20$) on ORR.
Conclusions: Spontaneous regressions are seen across all advanced solid tumors. Some malignancies demonstrated higher rates of spontaneous regressions and may be relatively immunotherapy responsive.

1. Introduction

Spontaneous regression (SR) of malignancies is defined as the partial or complete disappearance of a tumor proven by microscopic examination, in the absence of any substantial treatment, or in the presence of therapy that is considered inadequate (Everson, 1967; Cole and Everson, 1966). Everson and Cole retrospec-

* Corresponding author at: UAB Comprehensive Cancer Center, 1802 6th Ave. S., NP2540B, Birmingham, AL 35294. United States. Fax: +1 205 975 3910.
E-mail address: gsonpavde@uabmc.edu (G. Sonpavde).
[1] Authors have equal contribution in this manuscript.

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tively observed reports of 176 patients, seen from 1908 to 1966, who exhibited SR. Renal cell carcinoma (RCC) and melanomas, immunotherapy-responsive malignancies, were most frequently associated with SR (Cole and Everson, 1966). Since then, there have been several retrospective case reports and series in the literature describing SR in a variety of cancers, including HPV-induced cervical intraepithelial neoplasia (Kadish et al., 2002), cholangiocarcinoma (Yoshimitsu et al., 1996), melanoma (Tran et al., 2013; Bramhall et al., 2014), hepatocellular carcinoma (Misawa et al., 1999; Harada et al., 2010; Meza-Junco et al., 2007; Oquiñena et al., 2009; Arakawa et al., 2008; Del Poggio et al., 2009; Lim et al., 2014), RCC (Crisci et al., 2008), esophageal carcinoma (Kubota et al., 2003), non-small cell lung cancer (NSCLC) (Hwang et al., 2013), merkel cell carcinoma (Brown et al., 1999; Torroni et al., 2007; Vesely et al., 2008; Karkos et al., 2010), small-cell lung cancer (Lee et al., 2008; Hirano et al., 2007; Horino et al., 2006; Gill et al., 2003; Zaheer et al., 1993; Nakano et al., 1988; Iwakami et al., 2013) and squamous cell lung cancer (Choi et al., 2013).

The incidence of SR of cancer is difficult to quantify, but is estimated to occur in 1 in 60,000–100,000 cancer patients (Everson, 1967). However, estimates of the rate vary widely, and many cases are probably not reported. Difficulties involved in establishing what criteria must be met in order for a specific case to constitute an instance of SR further complicate determining the true frequency of this phenomenon (Challis and Stam, 1990). We hypothesized that systematic prospectively collected information on response rates for a broad spectrum of malignancies receiving no anti-cancer therapy may essentially reflect and inform on SRs and selection of the most suitable tumors for trials of immunotherapy, i.e., tumors with the highest response rates when receiving no anti-cancer therapy may be biologically most prone to response to up-regulation of the immune system. Here we conducted a meta-analysis of response in control arms of available randomized clinical trials (RCT), which administered either placebo or no anti-cancer therapy, in adults with advanced solid tumors.

2. Methods

2.1. Selection of studies

An independent review of citations in the English language from PubMed/Medline from January 1980 to June 2014 was conducted. Keywords included in the search were "placebo"; "best supportive care" and "cancer". The "randomized controlled trial" option was selected to narrow the search. Abstracts and virtual meeting presentations from major conferences—American Society of Clinical Oncology (ASCO); European Society of Medical Oncology (ESMO); and American Association of Cancer Research (AACR); were also reviewed. Databases from clinicaltrials.gov were also searched. RCTs with at least one arm containing no anti-cancer therapeutic agent(s) (placebo; observation; supportive care) were selected. Trials not reporting tumor responses were excluded. Trials using either the Response Evaluation in Solid Tumors (RECIST 1.0 or 1.1) or World Health Organization (WHO) criteria were used (Therasse et al., 2000; World Health Organization, 1979; Eisenhauer et al., 2009). Trials containing chemotherapy in the best supportive treatment arm were excluded; however those containing palliative radiation therapy were included since, lesions in radiated fields are not considered evaluable for response. Study quality was assessed by using the Jadad ranking system (Jadad et al., 1996).

2.2. Data extraction and clinical end points

The variables extracted are shown in Table 1. We also captured the rates of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Generally, radiographic monitoring was conducted every 6–12 weeks. The line of therapy was recorded, and prior therapy administered was recorded when the setting was ≥second line. Trials evaluating maintenance therapy following first-line therapy were classified as second-line trials. If some patients in a trial had received prior first line agents, whereas others had not, first-line therapy was recorded as administered to "some" patients. Whether patients were required to have PD at the time of trial entry was recorded; while most trials required PD at baseline, second-line maintenance trials required absence of PD at baseline. The version of the response criteria, RECIST (1.0 or 1.1) or WHO, used was also captured.

2.3. Statistical analysis

Statistical analyses were performed by using R statistical software, version 3.0 (Schwarzer, 2013; Viechtbauer, 2010). The proportion of evaluable patients with CR, PR, SD and PD were derived for each trial and used to calculate the overall response rate (ORR: CR + PR), which was the primary clinical endpoint, and the disease control rate (DCR: CR + PR + SD) as a secondary clinical endpoint. For studies reporting zero patients with either CR or PR, the classic half-integer correction was applied.

For the meta-analysis, both the fixed-effects model and the random-effects model were considered. The latter was calculated with the method of DerSimonian and Laird, which considers both inter and intra-trial variation (DerSimonian and Laird, 1986). Statistical heterogeneity among studies included in the meta-analysis was assessed using the Cochrane's Q statistic, and inconsistency was quantified with the I^2 (I-squared) statistic, which is used to describe the percentage of total variation across studies that is due to heterogeneity rather than chance; a value of 0% indicates no observed heterogeneity, while larger values between 0% and 100% show increasing heterogeneity (Higgins et al., 2003). The assumption of homogeneity was considered invalid for p-values <0.1, and in this case, we reported summary estimates from the random-effects models.

We used meta-regression to determine whether the rates of ORR and DCR were significantly affected by the histological pattern. We also conducted a subgroup analysis to determine whether these rates were different for first-line studies as compared to ≥second-line studies, or for studies requiring PD vs. absence of PD at baseline. Trials in which some patients had received prior therapies whereas others did not, were excluded from the subgroup analysis examining ORR and DCR based on line of therapy. Finally, potential publication bias was evaluated through funnel plots with the Egger test using an arcsine transformation (Rucker et al., 2008). A two-tailed p-value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Search results

Our search yielded a total of 125 potentially relevant RCTs containing at least one arm with no anti-cancer therapy. Fig. 1 represents the selection process: 64 trials were excluded for not using the RECIST 1.0, RECIST 1.1 or WHO criteria to measure responses, or for not reporting response outcomes. The remaining 61 trials were considered highly relevant for the study (Table 1) (Demetri et al., 2013a,b, 2006; Grothey et al., 2013; Elisei et al., 2013; vanderGraaf et al., 2012; Sternberg et al., 2010; Ahn et al., 2013; Leboulleux et al., 2012; Lee et al., 2012a,b; Del Campo et al., 2011; Miller et al., 2012; Wu et al., 2013; Mulders et al., 2012; Van Cutsem et al., 2007; Shepherd et al., 2005; Thatcher et al., 2005; Ledermann et al., 2012; Gaafar et al., 2011; Goss et al., 2009; Zhang et al., 2012; Raymond