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Usefulness of prestudy assessment of patient willingness to undergo tissue biopsy for correlative studies in a melanoma vaccine trial

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Abstract

Background—Performing biopsies for correlative studies in cancer trials raises ethical and regulatory concerns and may impact trial accrual negatively. However, strategies to address these concerns remain largely unexplored.

Purpose—We sought to assess the perceived risk of mandatory tissue biopsies to be performed for research purposes as part of a clinical trial of a melanoma vaccine by administering a pretrial accrual assessment questionnaire in the population of interest. Furthermore, we explored how such survey data may be used to address potential concerns of regulatory and funding organizations that may not be able to assess the risks of those biopsies.

Method—A total of 91 melanoma patients, similar to potential participants in a melanoma vaccine pilot study, scored their willingness, on a 9-point Likert scale, to participate in vaccine trials involving no skin biopsy versus a skin biopsy resulting in a 3-, 6-, or 12-cm scar. The vaccine trial was performed with skin biopsies leaving a 6-cm scar. Accrual rate was assessed and that accrual was compared to the accrual of two similar vaccine trials without biopsy requirements.

Results—A total of 95% of the participants expressed willingness to enter a vaccine trial (likely to highly likely). This proportion decreased to 74%, 63%, and 59%, respectively, for vaccine trials requiring skin biopsy leaving a 3-, 6-, or 12-cm scar. The trial was designed with an estimated 40% decrease in accrual rate compared to prior studies (2 participants expected/month). The resulting trial with a 6-cm biopsy exceeded that accrual rate estimate and had a similar accrual rate to vaccine trials without a biopsy (4.1 vs 2.7–4.6 participants/month).

Limitations—Potential limitations of this study include the exclusion of some questionnaire responses and the post hoc nature of the analysis.

Conclusion—Willingness to participate in vaccine trials was decreased by the requirement for skin biopsy, but the size of the biopsy was less of a deterrent than expected. Findings from brief surveys may aid in risk assessment during regulatory review, predict acceptability of tissue

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Conflict of interest

The authors have no conflict of interest to disclose.

collection for correlative studies, and support regulatory approval and meeting accrual goals of the study.

Introduction

With an ever-increasing arsenal of tools to investigate biologic processes in tissue, direct study of tissue from patients undergoing various treatments for cancer has the potential to increase dramatically our understanding of response to those treatments. Furthermore, incorporation of tissue correlative studies from patients enrolled in therapeutic clinical trials allows trial design using biologically based endpoints, which may be superior to traditionally utilized endpoints in some cases. This strategy has proven feasible and especially useful in early-phase trials of molecularly targeted agents [1,2].

As promising as this strategy may be, incorporating mandatory biopsy for correlative study in clinical trials presents ethical dilemmas and has been met with some resistance by governing bodies [3]. A recent survey of stakeholders in such clinical trials found that Institutional Review Boards (IRBs) and oncologists have a lower threshold for risk and anticipate a higher level of anxiety related to a biopsy for patients than patients actually report during participation in such trials [4]. Correcting such overestimation of patient anxiety may prevent delays in trial funding and approval. Recent data demonstrate that long clinical trial development time portends a lower likelihood of successful trial accrual; thus, minimizing such delays is of critical importance [5].

Studies also demonstrate that up to 38%–53% of national clinical trials studied may fail to meet their minimum accrual goals [5,6]. Obtaining data regarding potential accrual during a clinical trial's development stage may inform designers' decisions regarding target accrual numbers and expectations regarding the rate of accrual [6]. This information is particularly critical in trials that incorporate aspects that could be viewed by potential participants as undesirable.

In any clinical trial, there is potential risk and potential benefit; measuring and balancing them is always challenging for investigators and regulatory bodies. Assessing benefit includes evaluation of the scientific value of the proposed studies; for tissue biopsies or blood draws, this evaluation should include assessment of the rationale for the correlative studies to be done with the tissue, the alternatives to the proposed methods, and the need for the quantity of tissue or blood to be collected. Such assessments fall squarely within the expertise of the investigators, the IRB members, and personnel of the Food and Drug Administration (FDA). However, the assessment of risk of tissue biopsy may be measured best by those in whom such biopsies have been performed. We posit that when the primary risk is subjective, such as pain or cosmetic effect, studying the intervention in a population that has experienced the intervention is optimal for assessing risk. In particular, patients with melanoma have almost always undergone wide excisions of skin and subcutaneous tissue at the site of the melanoma, leaving incisions 6–15 cm in length. Thus, they are arguably optimal respondents for a survey to aid in estimating the risk:benefit ratio of the tissue sampling from the patient perspective. Herein, we present the successful use of patient query data to direct an assessment of the risk of mandatory tissue biopsies for research purposes

performed as part of a clinical trial of a melanoma vaccine. These and similar data may be useful to address potential concerns raised by funding and regulatory organizations who may not have the ability to assess the risks of biopsies or other potentially undesirable procedures directly.

Methods

MEL 48 trial

MEL 48 (University of Virginia, NCT00705640) was a single-institutional two-arm pilot study of 36 patients with resected American Joint Committee on Cancer (AJCC) stage IIB–IV melanoma undergoing treatment with MELITAC 12.1 (50 µg of each of 12 class I major histocompatibility complex (MHC) restricted melanoma peptides (MPs) and 100 µg of a tetanus helper peptide) emulsified in an incomplete Freund's adjuvant (IFA; Montanide ISA-51 adjuvant). Participants underwent vaccination once every week, for 6 weeks on an extremity clinically uninvolved with melanoma and at a second 'replicate' site. All participants received MELITAC 12.1 plus IFA but were divided into two groups: either receiving MELITAC 12.1 plus IFA at the replicate site or IFA alone at the replicate site. In order to investigate factors at the injection site with respect to time, within each study group, participants underwent a surgical biopsy of the replicate site performed at one of five possible times: day 1, 8, 22, 50, or 85. Results of the trial and correlative studies performed on the replicate vaccine sites have been reported elsewhere [7] and are not addressed here.

Vaccine site biopsy size

Prior studies at our institution were completed using punch skin biopsies, which provided limited tissue that was inadequate for some of the desired correlative studies, such as flow cytometric analysis and functional cellular assays. Thus, a biopsy size of 2 cm in diameter and 4–6 cm in length was proposed in order to provide sufficient tissue for analysis; biopsy incisions of this size could be closed without requiring a skin graft or other extraordinary measures for wound management.

Initial review of protocol

When the MEL 54 protocol was submitted for IRB approval, it was criticized for concerns about the requirement for the large tissue excision (6 cm) for correlative studies with resulting potential for poor accrual. Also, when the funding application for this trial was reviewed at the National Institutes of Health (NIH), similar concerns were voiced, and the study was not funded. Thus, we conducted a survey of melanoma patients to gain further information regarding patient acceptance of a clinical trial with biopsy for correlative studies.

Patient questionnaire

After obtaining University of Virginia IRB approval, a survey was mailed to a convenience sample of 100 patients with a diagnosis of melanoma from a single institution. These patients were in clinical follow-up and previously had expressed a willingness to receive questionnaires for research purposes. The questionnaire outlined the proposed clinical trial regimen and expected toxicities (see Appendix 1). It consisted of four questions inquiring

how likely (on a Likert scale of 1 (highly unlikely) to 9 (extremely likely)) a patient would be to participate in a melanoma vaccine trial without a skin biopsy or with a biopsy with a resulting surgical scar that would range from 3 to 12 cm. These questions were arranged with no biopsy first, then in descending order of size (largest to smallest). Also queried was whether the subject was a current or prior participant in a vaccine trial. The questionnaire was administered by mail in a paper format and returned in an anonymous fashion. NIH and IRB deadlines placed a time constraint on collecting survey data; thus, only one mailing was utilized. Two to three weeks were allowed for response prior to the initial data analysis. A second analysis that included all data from initial and later questionnaires was performed and is reported separately. The principal investigator (C.L.S.) performed the initial analysis and was responsible for decisions regarding data exclusion. Several responses were judged to be inconsistent, for example, the reported likelihood of participation was higher for larger sized biopsies than smaller biopsies and were excluded from the analyses. Proportions of respondents indicating each level of Likert scale scores of biopsy acceptability were compared between various biopsy sizes and between any biopsy versus no biopsy by using chi-square tests.

Clinical trial accrual

Actual time to complete accrual for the MEL 48 trial was recorded and was compared to accrual times from two prior melanoma vaccine trials, designated MEL 43 and 44, which required participant blood draws for correlative studies but did not require tissue biopsies [8,9]. MEL 43 was a phase II study of a vaccine comprising a mixture of 12 MPs and a tetanus helper peptide; participants were randomized to receive IFA or IFA plus granulocyte macrophage colony stimulating factor (GM-CSF) as the adjuvant [8]. MEL 44 was a phase I/II study of a vaccine comprising a mixture of 12 MPs administered in GM-CSF in IFA, with patients randomized to receive the 12 MPs in combination with a tetanus toxoid-derived helper peptide with or without a single pretreatment with cyclophosphamide or to receive the 12 MPs in combination with a 6 melanoma helper peptide (6-MHP) mixture with or without a single pretreatment with cyclophosphamide [9]. Both trials were open to patients with resected AJCC stage IIB–IV melanoma. Both were multicenter trials; however, enrollment goals and attainment from only our institution were assessed for the present analysis. These vaccine trials were chosen for comparison due to similar enrollment criteria and temporal proximity to the MEL 48 trial.

Results

Participant characteristics

Of the 100 patients who agreed to be contacted, 50% were stage IIB–IV, and thus would have been eligible for screening for the MEL 48 trial. A total of 92% of the participants had previously undergone wide local excision with at least a 1-cm margin (resulting in at least a 3-cm scar) as part of their clinical care. The remaining 8 patients were stage III or higher at initial presentation and thus did not undergo wide local excision.

Response rate to questionnaire about participation in clinical trials

Figure 1 shows the questionnaires returned and those excluded. In the period before resubmission of the grant proposal and protocol, 52 participants returned questionnaires, 36 of which contained some evaluable data. Of the 100 questionnaires mailed, 91 were returned; 62 questionnaires were completed at least partially. Upon review of the responses by the principal investigator, 7 questionnaires had answers that were not meaningful (i.e., likelihood of participation reported to increase with larger biopsy) and were eliminated from data analysis. Of the remaining partially completed questionnaires, 10 of the 12 answered the questions on the first page only (Figure 1).

Likelihood of participation by biopsy size

Table 1 summarizes the survey findings for the first 52 patients; Table 2 summarizes the data for all 91 respondents. The presence of a skin excision in a vaccine trial decreased the proportion of patients answering likely to highly likely to participate by 22% ($p = 0.05$) for the initial respondents, and 21% for all respondents ($p = 0.003$). In contrast, there were smaller decreases in the proportion of patients answering likely to highly likely to participate in trials with increasing sizes of skin excision, decreasing 10% from 3 to 6 cm, and only 4% from 6 to 12 cm for the initial respondents, with similar decreases of 11% and 4%, respectively, for all respondents; none of the differences were statistically significant (Tables 3 and 4).

Use of the data

As previously indicated, the initial IRB submission of the MEL 48 trial and NIH grant application were met with concern due to the effect of the biopsy size on patient accrual. After the questionnaire data were shared with the IRB and with the NIH reviewers on resubmission, IRB approval and NIH funding were obtained. The data also were incorporated in the Investigational New Drug (IND) application.

Clinical trial accrual

The findings of the questionnaire suggested that the accrual rate was likely to be about 60% of the accrual rate to trials without tissue biopsies. Based on prior experience and this estimate, we predicted accrual on the MEL 48 trial at 2 participants/month. Table 5 summarizes actual accrual results of the MEL 48 trial and two nonbiopsy-related vaccine trials MEL 43 and MEL 44, all of which met accrual goals. Actual accrual of 4.1 participants/month exceeded the expectation and was similar to that of prior trials that did not include skin excisions for correlative studies (Table 5).

Discussion

Designing and implementing a clinical trial requires assessment of the risks and potential benefits of the trial. Clinical trials with correlative studies are critically needed to improve care of cancer patients; however, correlative studies invariably require collection of blood and/or tissue biopsies. Each of these methods of sample acquisition carries some risk, inconvenience, or discomfort for the patient, which can negatively affect patient accrual. To

explore these issues prior to final approval of our trial, we sought input from a convenience sample of patients we believed would be well suited to address those questions.

Findings from a survey of melanoma patients indicated that requiring a tissue biopsy for correlative studies in a melanoma vaccine trial decreased a potential participant's stated likelihood of participation; however, the size of the biopsy, in the range assessed, appeared to be of less concern. The successful accrual of the MEL 48 trial at a rate similar to earlier trials without a biopsy requirement further demonstrated the willingness of patients to enter such trials. Although these are interesting findings on their own merits, perhaps more important is the value of assessing trial participation as a tool to guide trial design and estimate the likelihood of completion of trial accrual within a reasonable time interval.

In an evaluation of factors associated with closure due to inadequate accrual, Schroen *et al.* [6] found that trials that conducted a pretrial accrual assessment were significantly more likely to reach sufficient accrual. However, in a recent survey of study chairs and lead statisticians from 248 National Cancer Institute–sponsored trials, surveys or focus groups of prospective participants were perceived by study personnel to have no influence on accrual predictions [10]. Our experience would seem to refute this prevailing sentiment. In the case of MEL 48, the trial had to balance obtaining enough vaccine site tissue to perform the indicated studies while maximizing the chances of adequate patient enrollment. Our survey provided valuable data to suggest that the selected biopsy size would not prevent study completion. Furthermore, the data collected strengthened the protocol's validity in the eyes of the regulatory and funding bodies, which may have saved time spent in the approval process despite the time invested in conducting the survey.

Our accrual assessment required minimal effort and time, but the process could be made more efficient. This study used regular mail to deliver questionnaires; a few weeks were required for responses. Using email and available online survey services, similar studies could be done within a few days.

Limitations

There are some limitations of the presented data. First, the post hoc nature of our analysis prevents assessment of the influence of various demographic factors or the location of the proposed biopsy site on each patient's willingness to participate. For example, it is possible that certain groups, for example, younger women, would be less likely to enroll in a trial requiring a larger biopsy or would be less willing to undergo biopsy on the upper extremity rather than the lower. Questions regarding age, gender, and stage of disease were not included in the questionnaire nor was the option of upper versus lower extremity biopsy. Second, our questionnaire asked for likelihood of participation on a Likert scale, but the actual decision to enroll in a trial is binary. Likewise, patients are not often given the opportunity to choose between trials with small variations in the study procedures, as they were in this survey with multiple biopsy sizes. Presenting multiple possibilities may have resulted in a 'bargaining' effect, where one possibility may have seemed more acceptable in comparison to others than it would have otherwise. A further limitation is that we compared

accrual among vaccine trials; however, we have not addressed any other potential differences in the trials that may have affected accrual rates.

The questionnaire itself had several limitations that are potentially addressable in future studies. The finding that some patients completed only the first two questions demonstrates a flaw in the questionnaire design. Presumably, these patients did not see the second page of the questionnaire, as these patients also did not complete the question regarding their current participation status in vaccine trials. Also, though we explain the use of the biopsied tissue and specify that the questionnaire relates to a clinical trial, we did not explicitly state that the biopsies were nondiagnostic and nontherapeutic. Confusion regarding this issue may provide an alternative explanation to why several respondents indicated preference for a larger biopsy size. We also acknowledge that the language in our questionnaire could possibly have been more technical than needed; we recommend that questionnaires be as clear as possible for a lay audience population.

Finally, we make no attempt to address the issue of ‘reluctant consent’, that is, clinical trial participants agreeing to unwanted procedures or diagnostics in exchange for access to experimental treatments. This issue may play a role in studies, including tissue biopsy; however, it should be noted that blood draws for correlative studies also may be unwanted by patients but are widely employed in clinical trials. Although widespread incorporation of such unwanted aspects of clinical trials does not justify their ethical inclusion in new trials, it demonstrates that this issue is commonly encountered and nevertheless questions about ‘reluctant consent’ go unresolved.

Acknowledging these limitations, we believe that incorporation of data directly from patients similar to potential participants, who had experience with the proposed biopsy, had a positive role in trial design and that continued development and use of similar assessment tools is warranted, particularly in trials incorporating nonclinical biopsies or other aspects that may be expected to diminish the willing participation of eligible patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Trial Registration: MEL 48 (University of Virginia, NCT00705640).

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References

1. Dowlati A, Haaga J, Remick SC, et al. Sequential tumor biopsies in early phase clinical trials of anticancer agents for pharmacodynamic evaluation. *Clin Cancer Res.* 2001; 7(10):2971–76. [PubMed: 11595684]
2. Brown AP, Wendler DS, Camphausen KA, Miller FG, Citrin D. Performing nondiagnostic research biopsies in irradiated tissue: A review of scientific, clinical, and ethical considerations. *J Clin Oncol.* 2008; 26(24):3987–94. [PubMed: 18711189]
3. Helft PR, Daugherty CK. Are we taking without giving in return? The ethics of research-related biopsies and the benefits of clinical trial participation. *J Clin Oncol.* 2006; 24(30):4793–95. [PubMed: 17050863]
4. Agulnik M, Oza AM, Pond GR, Siu LL. Impact and perceptions of mandatory tumor biopsies for correlative studies in clinical trials of novel anticancer agents. *J Clin Oncol.* 2006; 24(30):4801–07. [PubMed: 17050865]
5. Cheng SK, Dietrich MS, Dilts DM. A sense of urgency: Evaluating the link between clinical trial development time and the accrual performance of cancer therapy evaluation program (NCI-CTEP) sponsored studies. *Clin Cancer Res.* 2010; 16(22):5557–63. [PubMed: 21062929]
6. Schroen AT, Petroni GR, Wang Hongkun, et al. Preliminary evaluation of factors associated with premature trial closure and feasibility of accrual benchmarks in phase III oncology trials. *Clin Trials.* 2010; 7(4):312–21. [PubMed: 20595245]
7. Schaefer JT, Patterson JW, Deacon DH, et al. Dynamic changes in cellular infiltrates with repeated cutaneous vaccination: A histologic and immunophenotypic analysis. *J Transl Med.* 2010; 8:79. [PubMed: 20727190]
8. Slingluff CL Jr, Petroni GR, Olson WC, et al. Effect of granulocyte/macrophage colony-stimulating factor on circulating CD8+ and CD4+ T-cell responses to a multi-peptide melanoma vaccine: Outcome of a multicenter randomized trial. *Clin Cancer Res.* 2009; 15(22):7036–44. [PubMed: 19903780]
9. Slingluff CL Jr, Petroni GR, Chianese-Bullock KA, et al. Randomized multicenter trial of the effects of melanoma-associated helper peptides and cyclophosphamide on the immunogenicity of a multi-peptide melanoma vaccine. *J Clin Oncol.* 2011; 29(21):2924–32. [PubMed: 21690475]
10. Schroen AT, Petroni GR, Wang H, et al. Challenges to accrual predictions to phase III cancer clinical trials: A survey of study chairs and lead statisticians of 248 NCI-sponsored trials. *Clin Trials.* 2011

Figure 1.

Questionnaires returned (N = 52). Numbers in parentheses represent questionnaires returned prior to the initial data analysis, that is, prior to resubmission.

Table 1

Number (%) of initial respondents reporting specified likelihood to enroll in a cancer vaccine trial with or without a requirement for skin excision for correlative studies (N = 52)

Size of skin excision	N	Likely to highly likely (scores = 5-9)	Moderately likely to highly likely (scores = 7-9)	Highly likely (score = 9)
No skin excision	36	33 (92%)	23 (64%)	20 (56%)
3-cm scar	30	21 (70%)	12 (40%)	8 (27%)
6-cm scar	30	18 (60%)	11 (37%)	6 (20%)
12-cm scar	36	20 (56%)	13 (36%)	6 (17%)
Excluded from analysis	16	–	–	–

Table 2

Number (%) of all respondents reporting specified likelihood to enroll in a cancer vaccine trial with or without a requirement for skin excision for correlative studies (N = 91)

Size of skin excision	N	Likely (score = 5) to highly likely (score = 9)	Moderately likely (score = 7) to highly likely (score = 9)	Highly likely (score = 9)
No skin excision	62	58 (95%)	42 (69%)	33 (54%)
3-cm scar	53	39 (74%)	25 (47%)	15 (28%)
6-cm scar	52	33 (63%)	19 (37%)	12 (23%)
12-cm scar	61	36 (59%)	23 (38%)	12 (20%)
Excluded from analysis	29	–	–	–

Table 3

The difference in percentage of respondents with scores in the specified ranges between specified biopsy sizes among the first 52 respondents (p-values from chi-square tests)

Likelihood of participation	No biopsy versus 3-cm scar (p)	3-cm scar versus 6-cm scar (p)	6-cm scar versus 12-cm scar (p)
Likely to highly likely (scores = 5–9)	22% (0.05)	10% (0.59)	4% (0.94)
Moderately likely to highly likely (scores = 7–9)	24% (0.09)	3% (0.98)	1% (0.86)
Highly likely (score = 9)	29% (0.38)	7% (0.74)	3% (0.87)

Table 4

The difference in percentage of respondents with scores in the specified range between specified biopsy sizes for all respondents (p-values from chi-square tests)

Likelihood of participation	No biopsy versus 3-cm scar	3-cm scar versus 6-cm scar	6-cm scar versus 12-cm scar
Likely to highly likely (scores = 5–9)	21% (0.003)	11% (0.32)	4% (0.81)
Moderately likely to highly likely (scores = 7–9)	22% (0.03)	10% (0.40)	–1% (0.93)
Highly likely (score = 9)	26% (0.009)	5% (0.72)	3% (0.87)

Table 5

Accrual rates in three melanoma vaccine trials with or without required tissue biopsy

Trial ID	Eligibility stage	Start date	Closure to accrual date	Tissue biopsy required?	No. of participants enrolled	Months to complete accrual	Mean accrual rate per month
MEL 43	IIB–IV	15 September 2003	31 March 2005	No	82	18	4.6
MEL 44	IIB–IV	3 March 2005	12 February 2008	No	88	33	2.7
MEL 48	IIB–IV	23 May 2008	29 May 2009	Yes	45	11	4.1