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13. ABSTRACT (Maximum 200 Words)
The purpose of this award id to evaluate the: 1) Safety and toxicity of neo-adjuvant thalidomide therapy prior to radical prostatectomy in patients with locally advanced prostate carcinoma (PCa); 2) Efficacy of neo-adjuvant thalidomide treatment, as measured by the rate of tumor reduction/ PSA decline; 3) Qualitative measurements of the in vivo effect of thalidomide therapy on the Endothelial and Epithelial compartment. Significance: The ability to assess in vivo the effects of thalidomide as well as identify surrogate markers of anti-angiogenic activity is in valuable to the design of new effective therapies.

Prior to the DOD's final decision (April 2002) to sponsor the correlative studies proposed in the grant 18 patients had been entered in this study. Their clinical information is attached. Pending some additional HSRRB required amendments, the patients' research tissue was stored but the funds awarded were not used to perform any of the studies until we obtained the final DOD approval. After April 2002 (when DOD was cited as a partial sponsor) and until we solved all the remaining issues and obtained DOD clearance to proceed (9/2003) we held accrual in this trial. We have re-activated the study and are confident that we will complete patient accrual within 1 year. We are requesting a no-cost extension of 1 year to allow completion of the planned studies.

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Introduction

The purpose **of this award is to evaluate the:**

1) **Safety and toxicity of neo-adjuvant thalidomide therapy prior to radical prostatectomy in patients with locally advanced prostate carcinoma (PCa),** assessed by wound healing and peri-operative bleeding. Up to 40 patients will be treated in this study.
2) **Efficacy of neo-adjuvant thalidomide treatment,** as measured by the rate of tumor reduction / PSA decline while on thalidomide therapy;
3) **Qualitative measurements of the *in vivo* effect of thalidomide therapy on the**
   a) Endothelial compartment: (MVD, endothelial cell apoptosis, tissue and circulating (serum/urine) levels of pro-angiogenic molecules (VEGF, transforming growth factor b1 {TGFb1}, basic FGF) and IL-6, IL-8.
   b) Epithelial compartment: Apoptosis / proliferation in PCa cells, and correlate with pathological findings at the time of prostatectomy.

Our **hypothesis** is that neo-adjuvant treatment with thalidomide will inhibit neo-angiogenesis in the primary organ (prostate) as well as at sites of possible micrometastases and may reduce PCa recurrence post-operatively.

This design of neo-adjuvant angiogenesis inhibition is a useful strategy of identifying intermediate markers of activity, which may accelerate drug development.

Body

The Clinical Development of Thalidomide as an Angiogenesis Inhibitor Therapy for Prostate Cancer (PCa).

Task 1. **Assess the safety and toxicity** of neo-adjuvant thalidomide treatment in patients with locally advanced PCa who undergo RRP (months 1-20).

- Up to 40 patients with clinical stage T1c-T2c, Gleason score $\geq$ 7 and PSA>10 or clinical stage T3 will be treated with 6 weeks of thalidomide (escalating weekly from 200 mg/day up to 600 mg/day). If there is no evidence of disease progression at 6 weeks (by PSA and TRUS criteria), patients will be treated with 6 more weeks of thalidomide (600 mg/day) and then will proceed to RRP. Safety will be assessed using the endpoints of:
    a) excessive peri-operative bleeding (more than 5 units of PRBC transfusions during the first 24 hours post-operatively), or
    b) abnormal wound healing (fascia dehiscence).

Based on historical rates of 8% for excessive bleeding and 2% fascia dehiscence at RRP a maximum adverse event rate of .10 is desired.

Applying the monitoring criteria specified in the protocol, after each cohort of 4 patients has been treated and evaluated, the trial would be terminated if the observed [#successes]/[# patients evaluated] $\leq$ 0/16, 0/20, 0/24, 1/28, 1/32, or 2/36, or if the observed [#adverse events]/[# patients evaluated] $\geq$3/4, 4/8, 4/12, 5/16, 5/20, 6/24, 7/28, 7/32, or 8/36.

Accomplishements

This clinical trial has been approved by the U.T.-MDACC IRB.

Prior to the DOD's final decision (April 2002) to sponsor the correlative studies proposed in the grant 18 patients were entered in this study. Pending some additional HSRRB required amendements, the patients' research tissue was stored but the funds awarded were not used to perform any of the studies until we obtained the final DOD approval.

After April 2002 (when DOD was cited as a partial sponsor) and until we solved all the remaining issues and obtained DOD clearance to proceed (9/2003) we held accrual in this trial. We were able to solve all the issues including a major one, the re-imbursement for potential research-related injuries. Given that there were no moneys dedicated for this in this award and the fact that MDACC does not provide compensation for research-related injuries, we worked with Celgene and came to an agreement that Celgene will provide re-imbursement for injuries related to the investigation in this study (the use of thalidomide).

The protocol and consent have been amended accordingly and reviewed and approved by the DOD in September 2003. We were given permission and re-activated the study and are confident that we will complete patient accrual within 1 year.

Our experience with the 18 patients treated is outlined below and the adverse events observed in these patients were also submitted for the DOD's review in July 2003 (Attention Mr. Peter J. Marshall, CIP, Human Subjects Protection Scientist) prior to the final DOD approval.

Experience of the first 18 patients enrolled in the study.

Total number of patients entered: 18

Race:	Caucasian:	16
	African American:	1
	Hispanic:	1

Age (median, range): 60 (43-71)

Zubrod performance status:

0:	16 patients
1:	2 patients

Clinical Staging at study entry:

T1c:	1 patient
T2:	6 patients
T3:	11 patients

Gleason score at study entry:

7:	8 patients
8:	5 patients
9:	4 patients
10:	1 patient

Pre-treatment PSA (median, range): 13.4 (4.9-190.2)

Maximum tolerated thalidomide dose:

400 mg/day:	2 patients
500 mg/day:	1 patient
600 mg/day:	15 patients

PSA results on thalidomide therapy

$\geq$ 50% PSA decline*:	7 patients (39%)
Stable PSA:	8 patients (61%)
PSA progression:	0 patients (0%)

*: a $\geq$ 50% decline in serum PSA has been associated with "clinical benefit" in prostate carcinoma.

17 of the 18 patients enrolled were taken to the operating room for planned prostatectomy. Fifteen of these patients completed prostatectomy as planned.

3 patients did not have a radical prostatectomy, as explained below:

> 1: Prostatectomy was aborted because the prostate gland was adherent to the pubis symphysis. Lymph nodes were negative and the patient was treated with radiation therapy after the aborted prostatectomy
>
> 1: Prostatectomy was aborted when the patient was found to have macroscopically involved pelvic lymph nodes at the time of his surgery (confirmed by frozen section)
>
> 1: Patient was not taken to the OR because of an enlarging abdominal aortic aneurysm. Patient was not considered best served by prostatectomy and was referred to vascular surgeons, had the abdominal aortic aneurysm corrected and was then treated with radiation therapy.

Patients tolerated the prostatectomy very well. The average hospitalization time was 3 days (range, 1-4) post prostatectomy.

Only 2 patients required blood transfusions (2 units each) and none required platelets or fresh frozen plasma transfusions.

All but 3 patients were discharged home without a drain post-prostatectomy. Three patients required a drain post-operatively for 7, 14, and 14 days, respectively.

Adverse events reported to the MDACC-IRB were reviewed by the DOD in July 2003.

None of the patients treated experienced any of the adverse effects specified in the protocol (excessive peri-operative bleeding or abnormal wound healing) that would constitute reason for concern and possibly early stopping of the study.

Of the 15 patients who completed prostatectomy, 11 (73%) achieved an undetectable (<0.1) serum PSA post-operatively.

Four of the 17 (24%) patients who were taken to the OR had positive lymph nodes at the time of the surgery. This compares favorably to our prior experience with another angiogenesis inhibitor (TNP-470) in a similar patient population, where 45% of the patients had positive lymph nodes at the time of the surgery.

Task 2. **To assess the efficacy** of neo-adjuvant treatment with thalidomide in patients with locally advanced PCa who undergo RRP (months 1-24).

- This is a phase II trial of neo-adjuvant thalidomide prior to RRP in patients with newly diagnosed locally advanced PCa. The design of Thall, Simon and Estey (14-15) will be used. For the purpose of sample size determination and safety monitoring, **patient success, S, is defined as stable disease (no increase in tumor mass) at 6 weeks, followed by ≥ 25% tumor shrinkage, compared to baseline mass or ≥ 50% decline in serum PSA (with no tumor progression) at 12 weeks.** At 12 weeks, once S is evaluated, all patients will undergo RRP. The adverse event, A, pertains to surgery, and is defined as either excessive bleeding or fascia dehiscence (see task 1). **A success probability of .20 or larger will be considered clinically promising,** and **a maximum adverse event rate of .10 is desired.**

Accomplishements

The interim evaluation of the first 18 patients is included in the Task 1 section, above. As shown, 7 of 17 patients (39%) achieved ≥ 50% PSA decline during thalidomide treatment. This is very optimistic and favorable according to the pre-specified efficacy criteria in the protocol.

The trial is now re-activated and we expect to complete patient accrual within 1 year.

Task 3. **Obtain qualitative measurements of the *in vivo* effect of therapy** (months 1-36).

TRUS prostate tumor measurement and prostate biopsies will be obtained pre- treatment, at 6 weeks (biopsy optional at that time) and at the time of the surgery. Serum and urine samples will be obtained weekly x 3 weeks (during escalation phase of thalidomide), then at 6, 12 weeks, pre- and post-operatively. Serum PSA will be measured pre-therapy, at 6 and 12 weeks on therapy, 3 weeks post-RRP and every 3 months thereafter. Bone marrow (BM) aspirate and biopsy will be obtained pre- and post-treatment (optional) with thalidomide and the effect of the therapy on bone marrow endothelial cells will also be assessed. We will look at the effects of therapy on:

- **Endothelial compartment:**

- Prostate (cancer and normal gland) MVD will be assessed immunohistochemicaly by staining with anti-CD31 antibody (16). Correlate with Gleason score and compare matched pre- and post-treatment samples.
- Endothelial cell (EC) apoptosis in normal prostate, prostate cancer, bone marrow biopsy (by Dual fluorescent labeling technique in CD-31 positive cells [TUNEL])

- Expression of bFGF, VEGF by PCa epithelium and prostatic stroma (by immunohistochemistry and / or in-situ hybridization (5,6,17).
- Modulation of circulating endothelial markers (18-21) (serum: E-selectin and Thrombomodulin) by ELISA.
- Modulation of serum: VEGF, TGFb1, IL-6 / Il-8, urine: bFGF levels and BM supernatant: VEGF,
IL-6/IL-8 levels will be measured by ELISA (6,17, 22-24).

- **Epithelial compartment:**

- Tumor size (by TRUS)
- PSA modulation on thalidomide therapy and freedom from biochemical relapse after surgery.
- Apoptosis in prostate cancer cells (by TUNEL)
- Proliferation index of PCa cells (by PCNA or Ki67)

We will determine whether expression of tissue or circulating pro-angiogenic molecules and cytokines correlate with: a) pathological findings at surgery (Gleason score, MVD changes, pathologically organ confined prostate cancer, rate of positive surgical margins and / or lymph node metastases) and could serve as surrogate markers for antiangiogenic activity in prostate cancer.

Accomplishements

Pending evaluation of the pathology specimens of patients treated on study. This will be assessed when all patients are treated so that the tissue is handled once with the same technique.

Key Research Accomplishements

- Review of the study by the HSSRB, revisions made according to HSSRB recommendations and approved by MDACC
- Secure re-imbursement by private sponsor for potential research-related injuries.
- Re-activate the study.
- Interim evaluation of the first 18 patients treated shows that there were no serious adverse effects so far that would mandate stopping the trial. There is also preliminary evidence that pre-operative treatment with thalidomide monotherapy has biologic activity in locally advanced prostate carcinoma.

Unfortunately solving the re-imbursement issue proved to be the most time-consuming issue since there were no funds allowed in the award to cover for potential research-related injuries. We feel very confident that with these issues solved now, we can proceed with rapid patient accrual and complete the study within the next 2 years. We are requesting a no-cost extension of 1 year to allow completion of the planned studies.

Reportable Outcomes

See Safety and Efficacy analysis of the first 18 patients above.

Conclusions

It proved really very time-consuming to secure financial coverage for potential research-related injuries, but we learned from this process.

So far there were no serious adverse effects that would mandate stopping the trial.

There is preliminary evidence that pre-operative treatment with thalidomide monotherapy has biologic activity in locally advanced prostate carcinoma.

Since we were able to solve all the DOD/HSRRB issues in September 2203, we did not use any of the award money that we received for the correlative studies proposed. The money is kept available for the studies as we now proceed with the re-activation of the study. We are requesting a no-cost extension of 1 year to allow completion of the planned studies.

References