Original Version dated 17 May 2013

Low Dose Chemotherapy Versus Best Supportive Care in Progressive Pediatric Malignancies: Double Blind Placebo Controlled Randomized Study

Information provided by (Principal Investigator):

Sameer Bakhshi, All India Institute of Medical Sciences, New Delhi

ClinicalTrials.gov Identifier:NCT01858571

Purpose of the Study:

Many of the paediatric malignancies are not curable on progression on front line or 2nd line chemotherapy. Further therapy with conventional drugs imposes many side effects and decreases the QOL. The usual therapy offered to such patients is best supportive care. Metronomic chemotherapy can induce tumor stabilization or tumor responses in patients with cancer that are refractory or have relapsed after conventional chemotherapy. Whether metronomic therapy is better than best supportive care is not known. In order to do so, a study is required which may compare metronomic therapy with a placebo therapy on PFS and QOL in relapsed refractory cases of paediatric solid tumours who have failed at least two lines of chemotherapy.

HYPOTHESIS

The investigators hypothesize that metronomic chemotherapy in progressive paediatric malignancy will improve PFS and QOL. If validated, then this form for therapy will be an option for both the patients and the clinicians, who are left with just an option of best supportive care in such situations of progressive paediatric cancers despite multiple lines of chemotherapy.

Condition: Malignant Childhood Neoplasm.

Intervention: Drug: Low dose chemotherapy.

Phase: Phase 3

Study Type: Interventional

Study Design: Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Intervention Model: Parallel Assignment

Masking: Double Blind (Subject, Caregiver)

Primary Purpose: Treatment

Primary Outcome Measures: •Progression free survival

Secondary Outcome Measures: •Overall Survival

Other Outcome Measures: •Quality of life

•Bio marker of angiogenesis (VEGF), Thrombospondin-1

Eligibility:

Ages Eligible for Study: 5 Years to 18 Years

Genders Eligible for Study: Both

Inclusion Criteria:

1.Refractory/Progressive non hematopoietic extracranial solid tumours following treatment with at least 2 lines of chemotherapy.

2.Good performance status(at least ambulatory)

3.Age: 5-18 years

4.Recovered from all acute toxic effects of earlier therapy

5.Absolute neutrophil count > 1X 10^9/L

6.Absolute platelet count > 75 x 10^9/L

7.Normal renal functions

8.Serum bilirubin <1.5 times the upper limit of normal, and the serum aspartate aminotransferase and alanine aminotransferase < 5 times the upper limit of normal.

Exclusion Criteria:

1.Uncontrolled concurrent illness or active infection

2.Positive serology for human immunodeficiency.

3.Unable to swallow oral medication

4.Pregnant and breast-feeding

Arms

1. **ARM 1: Experimental: Low dose chemotherapy**

Alternating cycles of Cycle A and B (Each cycle includes 3 weeks of drug administration) with each drug rounded off to the nearest tablet/capsule size.

Cycle A

•Daily oral Thalidomide (at 3mg/kg)

•Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg BID for patients > 50 kg)

•Daily oral Etoposide (50 mg/m2/d)

Cycle B

•Daily oral Thalidomide (at 3mg/kg)

•Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg BID for patients > 50 kg)

•Daily oral Cyclophosphamide (2.5 mg/kg/d to a maximum of 100 mg/d) every 21 days

Drug: Low dose chemotherapy

Drug Code	Drugs	Cycle A (3 weeks)	Cycle B (3 weeks)
Cap1	Thalidomide (3mg/kg)	Daily	Daily
Cap2	Celecoxib 100 mg BD for pts < 20 kg, 200 mg BD for pts 20–50 kg, 400 mg BD for pts > 50 kg,	Daily	Daily
Cap3	Etoposide (50mg/m^2)	Daily	----
Tab4	Cyclophosphamide (2.5mg/kg)(max=100mg)	----	Daily

Table 1: Drug schedule used in the study.

2. **ARM2: Placebo Comparator and Best supportive care**

Placebo: Alternating cycles of Cycle A and B (Each cycle includes 3 weeks of drug administration)

•Capsules of same size and colour as used in metronomic therapy

Best supportive care

•Management of pain as per WHO standard for pain management

Baseline Assessment

1. Basic Blood investigations:

- Complete Blood Counts.
- Liver and Kidney Function tests

2. Radiological Investigations:

- Contrast enhanced scan of chest and involved site.

3. Assessment of biomarkers of angiogenesis

- Serum/ plasma sample to measure VEGF, bFGF, endostatin, and thrombospondin-**1** levels.

4. Assessment of QOL by PedsQL- Cancer Module (version 3)

Before Each Cycle

1. Basic Blood investigations:

- Complete Blood Counts.
- Liver and Kidney Function tests

Interim (Post 3 cycles: at 9 weeks) and (Post 6 cycles: at 18 weeks)

1. Basic Blood investigations:

- Complete Blood Counts.
- Liver and Kidney Function tests

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1. Assessment of QOL byPedsQL- Cancer Module (version 3)

Further Assessments: Every 3 monthly till Progression

1. Basic Blood investigations:

- Complete Blood Counts.
- Liver and Kidney Function tests

2. Radiological Investigations:

- Contrast enhanced scan of chest and involved site.

3. Assessment of QOL by PedsQL- Cancer Module (version 3)

Assessment at Time of Progression

Assessment of biomarkers of angiogenesis

- Serum/ plasma sample to measure VEGF and thrombospondin-**1** levels.

Statistical analysis:

Descriptive statistics such as mean, median, standard deviation and range will be used to describe baseline demographic and clinical profile of all patients. To see association between two categorical variables, Chi-square test will be used. To see association between two continuous variables, t-test or Wilcoxon rank sum test will be used. Survivals will be depicted using Kaplan Meier plots. Difference between groups will be analysed using log-rank test. Proportional survival at specific times will be determined using Kaplan Meier survival analysis. P-value <0.05 will be considered as significant. Data analyses will be performed using statistical software packages Stata 11.2.

Sample Size Calculation:

From an exhaustive review of literature, data on PFS in solid extracranial tumours paediatric tumours after failing two lines of treatment, without any further therapy is not available from anywhere. From our experience we know that most of such advanced patients will progress within few weeks to months time. Therefore, we make the modest assumption that 95% of such patients will progress by 6 months without therapy and a 20% improvement is a standard parameter for efficacy in oncology patients. With a 2 sided α of 5% and power of 80%, a sample size of 49 in each group would detect a 20% difference between the proportion of progression at 6 months between placebo arm (group 1) and metronomic (group 2) (95% vs 75%). Assuming loss to follow up of 15%, 54 subjects per group will be required. So, total of 108 patients are proposed to be randomized.

Ethics and Registration:

The study protocol was submitted to the Institute Ethics Committee and approval has been obtained. All patients were included in the study after informed written consent.

Enrollment: 108

Study Start Date: October 2013

First received: May 17, 2013

Last updated: July 12, 2016

Last verified: July 2016

Study Protocol Version 2: (dated 17 June 2014)

Changes highlighted in yellow.

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The investigators hypothesize that metronomic chemotherapy in progressive paediatric malignancy will improve PFS and QOL. If validated, then this form for therapy will be an option for both the patients and the clinicians, who are left with just an option of best supportive care in such situations of progressive paediatric cancers despite multiple lines of chemotherapy.

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Eligibility:

Ages Eligible for Study: 5 Years to 18 Years

Genders Eligible for Study: Both

Inclusion Criteria:

1. Refractory/Progressive non hematopoietic extracranial solid tumours following treatment with at least 2 lines of chemotherapy.

2. ECOG performance status (<=3) (at least patients ambulating with crutches or on wheel chair)

3. Age: 5-18 years

4. Recovered from all acute toxic effects of earlier therapy

5. Absolute neutrophil count > 1X 10^9/L

6. Absolute platelet count > 75 x 10^9/L

7. Normal renal functions

8. Serum bilirubin <1.5 times the upper limit of normal, and the serum aspartate aminotransferase and alanine aminotransferase < 5 times the upper limit of normal.

Exclusion Criteria:

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2. **ARM1: Experimental: Low dose chemotherapy**

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Cycle A

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•Daily oral Etoposide (50 mg/m2/d)

Cycle B

•Daily oral Thalidomide (at 3mg/kg)

•Daily oral Celecoxib (100 mg BID for patients < 20 kg, 200 mg BID for patients 20-50 kg, and 400 mg BID for patients > 50 kg)

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Table 1: Drug schedule used in the study.

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Placebo: Alternating cycles of Cycle A and B (Each cycle includes 3 weeks of drug administration)

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Best supportive care

•Management of pain as per WHO standard for pain management

The dose of medications in capsules have to be rounded off to the nearest capsule size. Instead of rounding off on the daily dose, the total dose over the week would be calculated and rounded off and divided over 5-6 days in a week. This is being done so as to prevent any extra dosing.

If any grade 3-4 toxicity occurs in the first course, then the dose for chemotherapy would be reduced in the subsequent course by 20%.

All toxicities and adverse effects of the drugs would be graded according to NCI common terminology criteria for Adverse Events version 4.03 (June 2010).

Baseline Assessment

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Primary Completion date (last date for data collection)