Version 6 12/10/207

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A novel method of improving the Therapeutic ratio of chemotherapy for Haematological and potentially other malignancies.

Montelukast in Myeloma. MOM trial.

Abstract

Chemotherapeutic agents which induce apoptosis are vital to killing cancer cells, however there are multiple mechanisms by which malignant cells avoid cell death from these agents. Inhibiting these 'pro- survival' mechanisms has the potential to result in greater response to existing chemotherapy. It is hypothesized that adding the Leukotriene inhibitor; Montelukast and Gemfibrozil to standard chemotherapy will improve the response of patients to this treatment. It is hypothesized that that this improvement will by multiple mechanisms including blocking the MRP-1 and MRP-4 mediated efflux of oxidised glutathione(GSSG) from the mitochondria, by downregulating bcl-2 and increasing both BAK and cyclic AMP. It is not in the scope of this study to determine a mechanism but to determine whether there is any therapeutic benefit in adding Montelukast.

Hypothesis

Montelukast will lead to increased therapeutic ratio by a number of different mechanisms.

1) Montelukast will increase the Mitochondrial Oxidised Glutathione (GSSG) concentration, resulting in a greater proportion of tumour cells killed by chemotherapy. 2) Montelukast will inhibit the translocation of leukotrienes into the cell nucleus, resulting in less chemotherapy toxicity in non-haematological tissues.

2) Montelukast will inhibit BCL-2 and promote BaK increasing the proportion of apoptosis in tumour cells undergoing chemotherapy. There also appears to be a caspase independent process of cell death.

3) Montelukast will increase haematological cell apoptosis by increasing Cyclic AMP in tumour cells.

4) By its knowneffect on Leukotriene signalling.

Introduction

ATP-binding cassette proteins (ABCC), also called multidrug resistant proteins (MRP) are a family of at least twelve transport proteins involved in the cellular efflux of anions across cell membranes[1]. They transport a variety of molecules including some chemotherapy agents, chemotherapy-glutathione conjugates, oxidised glutathione (GSSG), leukotrienes and cyclic nucleotides and reduced Glutathione (GSH)[2,3]

MRP by exporting a variety of intracellular anions out of the cytoplasm and organelles are important regulators of cell oxidation reduction homeostasis[4.]

The type of MRP expressed in cell membranes depends on the tissue of origin[5,6]. MRP are highly conserved in nature and are found in all eukaryotes and prokaryotes tested[7]. They have recently been described to occur on the mitochondrial membrane[8]. It is

predicted that inhibiting MRP transporters during a period of malignant cell stress, that mitochondrial dependent apoptosis can be enhanced[9].

Montelukast is a leukotriene inhibitor that is currently used in the treatment of asthma. It has been shown to inhibit the transporters MRP-1 (ABCC1)[10], MRP-2(ABCC2)[11] and MRP-4 (ABCC4).[10] There is great potential for Montelukast to inhibit other ABCC transporters as well as its effect on leukotriene receptors. Montelukast does not directly inhibit p-glycoprotein (MDR-1.)and therefore should not increase chemotherapy toxicity. [12]

Montelukast[13] is currently used and has shown to be safe when treating asthma with therapeutic doses of between 5 and 10mg. However, there is no toxicity at overdoses up to 60 times the standard dose in children(4mg/kg)[14]. No upper toxic dose has been established. It has a half-life of elimination of 4-5 hours and is rapidly absorbed in two to three hours orally[13]. It is metabolised rapidly by cytochrome P450 3A4 and 2C8.[15] Montelukast metabolism is inhibited by Gemfibrozil[15]. The metabolites are excreted in bile and not in urine. It has a volume of distribution of 10 litres. Its kinetics are linear up to a 50mg dose. It is inexpensive and off patent. It has few recognized drug interactions. The only toxicity identified are some neuropsychiatric symptoms which can occur at a standard dose.

Translating the in vitro effects of Montelukast the required oral dosing of Montelukast to see an effect in cancer patients is difficult. Studies have shown that incubating MRP-2 expressing cells with 20uM Montelukast for 30 minutes' leads to inhibition lasting hours[11]. This suggests that the drug is tightly bound to MRP-2 and the physiological response lasts much longer than the serum concentration. The standard therapeutic dose of Montelukast (10 mg) leads to a level of 0.5 to 1 micromolar. Unfortunately, there

has been no study on the minimal inhibitory concentration of Montelukast on either MRP-1 or MRP-4.

It is proposed that 20mg of Montelukast twice daily be administered with 200mg twice daily of Gemfibrozil. It is estimated that this will give steady state a plasma level between 10 and 30 micromolar. It is anticipated that this dosing will lead to an equivalent Area Under the Curve (AUC) to the inhibition of MRP-2 demonstrated in tumour cells in vitro. Due to the lack of observed toxicity of Montelukast in overdose, plenty of scope exists to increase Montelukast doses. The current proposed protocol dose is predicted to lead to concentrations of 5– 20 μM Montelukast for the duration of treatment

There is also evidence that the blockage of Leukotriene transport into the cell Nucleus by Montelukast protects non-haematological cells from oxidative apoptosis[17]. Off target tissues could therefore be relatively protected by the differential susceptibility to leukotriene mediated damage[18]

Background

1) Mechanism 1 Glutathione and Mitochondrial release of Cytochrome C

Glutathione (GSH) is small triamino acid peptide that is involved in reducing oxidized intracellular molecules[19]. By maintaining a reduced intracellular environment, risk of cell damage and death from toxic substances including Reactive Oxygen species (ROS) is reduced[19]. The level of intracellular Glutathione (GSH) is maintained by two mechanisms.

1) The conversion of oxidised Glutathione (GSSG) is enzymatically converted back to GSH by an NADPH dependent Glutathione reductase [20].

2) Oxidised Glutathione is also effluxed from the cell by a variety of ABCC proteins including MRP-1[21].

The effect of these cell processes is to maintain a high GSH to GSSG ratio, preventing cell damage and death[3]. Disrupting this ratio in malignant cells offers a mechanism of greater tumour cell death during treatment.

It is known that tumour cells rely on increased oxidation pathways to provide a proliferation advantage [22,23]. These pathways which maintain higher GSH levels are induced in tumour cells. Cancer cells have been shown to have increased Glutathione metabolism as well as increased efflux of (GSSG) through MRP[22]. There appears to be increased affinity for efflux of GSSG compared to GSH[44] contributing to a high intracellular GSH: GSSG ratio. [24,21,3] There is upregulation in the transcription of a range of transporters involved in glutathione transport (GSSG) within hours of administering chemotherapeutic agents.[25] This protects the cancer cells from apoptotic death induced by oxidative stress. It is proposed that the inhibition of GSH preserving measures will sensitise the tumour cells to treatment in comparison to tissues which do not completely depend on these processes for survival, resulting in greater apoptotic death.

It has been long known that lower levels of intracellular glutathione (GSH) is associated with increased apoptosis (cell death)[26]. It has recently been revealed that increasing intracellular oxidised glutathione (GSSG) can lead to the death of tumour cells[27]. The mechanism through which this occurs is likely to be the mitochondrial pathway of apoptosis.

In the mitochondria where apoptosis is triggered the GSH: GSSG ratio is tightly maintained at a ratio of around 100:1 [28]. Reducing this ratio induces the release of cytochrome c from the mitochondria resulting in cell death[29].

Glutathione (GSH) is actively pumped into the mitochondria, protecting it from oxidative damage. This process is mediated by BCL-2 and may be one of the reasons for the intrinsic resistance of malignant cells to apoptosis[30]. BCL- 2 is upregulated in many tumours. It is not known whether oxidised Glutathione (GSSG) is also pumped into the mitochondria by the same pathway, paradoxically if this was the case, BCL-2 could increase apoptosis in a state of cytoplamic oxidation. It has also been shown that BCL-2 is downregulated in an environment in which the cytoplasm is oxidised[31] can increase susceptibility to apoptosis. The pathway by which this occurs is unknown. Inhibiting BCL-2 function is known to increase apoptosis in myeloma and B-cell leukaemia[32]. BCL-2 is however upregulated in many malignancies [32].

MRP-1 is found on the mitochondrial membrane[8] of all human cells and is involved in efflux from the mitochondria[9]. It can be induced in tumours by cancer chemotherapy[9]. It is likely that glutathione (GSSG) is its natural substrate and acts to maintain mitochondrial redox potentials. Crucially, inhibiting mitochondrial MRP-1 provides a target by which mitochondrial induced apoptosis can bypass the anti-apoptotic effects of pro survival proteins such as BCL-2. I hypothesise that inhibiting mitochondrial MRP-1 by Montelukast during cancer chemotherapy will improve the ratio of tumour cells killed by any standard chemotherapy treatment.

Meechanism 2. .

It has recently been shown that in lung cancer cell lines that Montelukast decreases BCL-2 and increases BAK leading to increased apoptosis in lung cancer cells. The concentration

required was between 50 to 80 uM of Montelukast. The mechanism may be related to the predicted effect of Montelukast on GSSG and Cyclic AMP. It is highly possible there is another mechanism involved. It was shown by the autghors that cell death proceeded by a caspase 9 independent process.

Mechanism 3 Cyclic AMP.

Increasing cyclic AMP in both B-CLL and Multiple Myeloma has been shown to increase cell death by a BIM/BCL-2 dependent apoptotic pathway [36,33,37]. Cyclic AMP has also been shown to synergistically increase Glucocorticoid induced apoptosis[37]. Glucocorticoids increase the transcription of the pro-apoptotic protein BIM. Cyclic AMP's action is to activate BIM by phosphorylation. Activated BIM[38] then directly inhibits BCL-2 which in turn prevents Mitochondrial destabilization and cytochrome c release via BAX. The net effect of increasing cyclic amp in lymphoid malignancies should be to be 'pro apoptotic'. This has been demonstrated in patients with B-CLL. Due to the known differential effect of cyclic AMP in different cell types, it could be both neuroprotective, but toxic to lymphoid cells.

One target of neuroprotection could be peripheral nerves where increased cyclic amp is neuroprotective.

The intracellular concentration of cyclic AMP is determined by three mechanisms - production, efflux and breakdown. Cyclic AMP effluxes from the cell by mrp4 (ABCC4)[10] and mrp5 (ABCC5). It is broken down by phosphodiesterase [39]. Phosphodieserase inhibitors improve the survival of mice with lymphoma. It has also been shown to increase apoptosis in Humans with early stage CLL.

Montelukast blocks the mrp-4 efflux of cyclic AMP as well as being an inhibitor of phosphodiesterase. Furthermore, it increases the levels of other cyclic nucleotides such as cyclic-GMP. It is

hypothesized that Montelukast will augment apoptosis via the BIM pathway by increasing cyclic-AMP levels in haematological tumours.

Mechanism 4 Leukotrienes in Apoptosis.

Leukotriene C4 is an intracrine mediator of oxidative induced apoptotic cell death in non-haematopoietic cells[17]. Leukotrienes are transported into the nucleus during oxidative damage. Here they mediate the transcription of some pro-apoptotic proteins. Montelukast has been shown to block this process leading to lower cell death in some non-haematological cells. . It is hypothesized that adding Montelukast to chemotherapy for haematological malignancies will increase response whilst reducing toxicity in non-haematological tissues. Montelukast has also been shown to increase apoptosis in activated t-Cells. The mechanism is unknown however this finding could be exploited in t-cell malignancies where t-cell activation is prominent in a number of types including Angioimmunoblastic T- Cell lymphoma where activation is prominent.

Aim

It is predicted that the addition of Montelukast to standard validated cancer treatment will result in deeper remissions in patients with resistant as well as non resistant tumours.

It is anticipated that the improvement will be gained with lower toxicity.

Furthermore, a reversal of tumour pro-survival mechanisms is predicted to lead to deeper remissions. The hypothesis is easily testable due to the lack of known toxicity of Montelukast. It is hoped

that this leads to longer overall survival for patients alongside lower side effects and lower healthcare costs.

Proposal

It is proposed that Montelukast is administered during a short period of standard chemotherapy in patients with poor prognosis haematological cancers with a short life expectancy.

Multiple myeloma is an ideal tumour to test the effect of Montelukast as it responds well to Cyclophosphamide, Bortezomib Chemotherapy, Immunomodulatory agents and Corticosteroids[40,42]. There is no current cure for Multiple Myeloma.

The survival of patients was generally 2-3 years prior to the advent of more modern agents. Bortezomib is currently the gold standard in the treatment of Multiple Myeloma and has led to significant improvement in outcomes. There are however a significant proportion of patients who still do not respond to modern therapies[41]. There are other agents including Thalidomide and related compounds which have also increased the life expectancy of patients with multiple myeloma.

Bortezomib, a proteasome inhibitor induces apoptosis synergistically with alkylating agents and corticosteroids. Bortezimib acts to increase reactive oxygen species by preventing the breakdown of misfolded proteins[26]. The reactive oxygen species react with GSH to produce oxidised Glutathione (GSSG). Adding reduced Glutathione (GSH) abolishes the effect of Bortezomib, in vitro[26]. It is also known that the inhibition of BIM is one of the mechanisms resulting in Bortezomib resistance. Interestingly Cyclic AMP also increases Bortezomib induced proteasome inhibition.

The limiting toxicity of Bortezomib in phase 1 and 2 studies was neurological toxicity[40]. It is anticipated the increase in cyclic AMP will reduce Bortezomib neurological toxicity by reducing cell damage in peripheral nerves. Bortezomib cellular efflux is not affected by Montelukast which is MDR-1 dependent[12, 42.] As a result, Montelukast looks to be ideally suited to be used with Bortezomib/cyclophosphamide/dexamethasone[40] combinations.

Importantly Bortezomib is usually given in weekly and twice weekly doses, allowing for the very close monitoring of patients for signs of toxicity. This is vital in preventing the patient receiving significant harm from an unexpected side effects. It is predicted that the weekly regimen will add to the safety of the investigation.

Summary of patient treated with Montelukast with multiple Myeloma.

Initial Case Report: Outcome in solitary patient with poor response to initial therapy with off label use of Montelukast.

This patient will not be used in analysis. The patient was treated 'off label' due to rapid progression on conventional Cyclophosphamide/Thalidomide/Dexamethasone (CTD) while this proposal was being formulated. She will be subject of a case report.

Patient female age 65 with stage 3 myeloma. Patient presented with a combination of fractures, bone pain, anaemia 89 g/l and mild renal failure. Alkaline phosphatase was raised. EGFR was reduced to 33ml/min. Albumin 44g/l. A trace of kappa light chains was detected on EPG. Serum light kappa chains were elevated at 262mg/l, Kappa: lambda ratio of 120. Beta 2 microglobulin was

raised at 5.6. The bone marrow showed a nodular pattern of multiple myeloma (cd 138 positive) detected on the trephine. She was hydrated and placed on sodium bicarbonate. There was an improvement in renal function prior to chemotherapy with CTD.

She received 8 weeks' therapy with Thalidomide at 100mg per day, Dexamethasone 20mg weekly, Cyclophosphamide 100mg daily orally. During the period of therapy, the kappa light chain increased sequentially to 1100mg/L after 4 weeks and then to 1668mg/l at 8 weeks. The Kappa: Lambda Ratio increased from 120 to 930, EGFR was maintained 52ml/min. The neutrophils had dropped to 1.8. The anaemia was unresolved.

As a result of progressing on treatment the treatment was changed. Progressive disease on the CTD regimen occurs in less than 3% of multiple myeloma patients. The assessment of her likely overall survival was 9 -18 months at this stage due to poor response[41].

Bortezimib/cyclophosphamide/Dexamethasone and Montelukast was administered. Following 8 doses (2 cycles) the kappa light chain had decreased to 7.6 mg/l (normal) with a kappa lambda ratio was still elevated at 4.8. After 12 doses (3 cycles) the kappa: lambda ratio was also normal at 0.9. This is consistent with a complete response.

A bone marrow biopsy and urine EPG was performed to determine response. The bone marrow aspirate contained no visible plasma cells. Flow cytometry determined there was no mature b-cells or plasma cells detected at all. The bone marrow trephine displayed no evidence of multiple myeloma, including cd 138 positivity. Cd 138 positivity was present in 0.5% of Bone marrow cells using Immunohistochemistry of trephine. These cells were not monoclonal on kappa/ lambda staining. There were also groups of CD10 positive Haematogones suggesting that B-Cell reconstitution was taking place.

There was little toxicity. EGFR was stable at 56ml/minute. There was a large improvement in the patients general wellbeing. Haemoglobin improved to 109g/L. There was a transient thrombocytopenia down to 85x10^9/Litre. This rapidly recovered to over 200x1012/L in 1 week. Neutrophils had recovered to a normal level 2.9. There was no neutropenia during the treatment period. There was no hepatic or renal toxicity. She developed level 1 sensory paraesthesia affecting the tips of toes only (common after Thalidomide and Bortezomib). There was some mild hair thinning (cyclophosphamide). She developed fevers about 6 hours after each Bortezomib dose, (this occurs in 30% of patients on standard regime). No evidence of infection was detected and she subsequently received 4mg of dexamethasone after each dose of Bortezimib to prevent symptoms. She suffered an episode of Herpes Zoster on the left L3 dermatome in the post treatment period, which responded to antivirals, which is common in myeloma patients receiving treatment.

Treatment with this regimen led to a rapid and complete response (sCR) after having rapidly progressive disease on first line therapy, with no increase in toxicity above standard chemotherapy. She is now 18 months from diagnosis after having consolidation with high dose chemotherapy and PBSCT. She is well without evidence of relapse.

Her overall survival is now predicted to be in excess of 10 years, progression free survival (PFS) of 5 years43. The response was compared to the speed of response on standard VCD published in the literature in patients with relapsed refractory disease. No other patient in the pivotal VCD trial s with progressive disease responded so completely or promptly to so few cycles of treatment.

There are no registered trials in Australia or New Zealand or the International Trials Registry which use Montelukast to improve the results of Cancer chemotherapy. This study is completely novel.

The pilot study will test whether patient's response to standard chemotherapy treatment will be improved by Montelukast. It will also test whether there is any increase in known toxicity as well as any unanticipated toxicity by increasing the dose of Montelukast to 4 times the standard daily dose and reducing its excretion by adding a standard dose of gemfibrozil.

As previously explained there is little pharmacokinetic data to guide the dosing. The current dose of 50mg over a 24-hour period is an estimate using the AUC in the only experiment that has tested dose response. Plenty of scope exists to increase dose based on the pilot study.

The Pilot study was limited to 6 patients with an otherwise poor prognosis. This group of patients have the most to gain from a successful outcome and have the least to lose.

Methods.

Patient eligibility was restricted groups of patients based on poorer prognosis. These are classified as relapsed, resistant and poor responders to standard treatment. A daily dose of Montelukast +/- Gemfibrozil is added to a multitude of different standard treatment regimens.

The patients were explained the purpose of the study. Only after informed consent were they prescribed drugs. They were reviewed for response and toxicity and given updates on each clinic visit of

toxicity , results to date in other patients so that they had the option of withdrawing consent at any time.

Informed consent including the scientific rationale, was be provided to each subject. The consent will summarise potential benefits to the patient including;

Potential less side effects

Potential response and an increase in their life expectancy.

The consent included summarise the potential risks including:

Unanticipated toxicity including the risk of death.

Unanticipated toxicity resulting in disability or potential painful side effects.

A neurological assessment focusing on peripheral neuropathy will take place prior to the first administration. Any other toxicity will be recorded and graded according to accepted standards.

Patients are to be given 2 to 3 cycles of standard CyBorD chemotherapy. Patients meeting the eligibility criteria will be offered the study medications.

Determination of serological response was made every 4 weeks on study. Toxicity including Neurological, haematological, renal and hepatic toxicity was assessed weekly.

At the completion of the initial cycles adetermination by the treating physician was made to determin whether Montelukast could be added.

Dosing: 1) Montelukast 20mg twice daily was given twice daily while on treatment

2) Montelukast 10mg twice daily and gemfibrozil 200mg twice daily while on treatment

3) Montelukast 20mg twice daily and gemfibrozil 200mg twice daily was given on treatment.

Toxicity

There were no episodes of renal or hepatic toxicity in any patient. Interestingly hepatic abnormalities appeared to improve on the study drugs.

One patient developed anaemia on therapy at a level that was commensurate with the anaemia from the cytotoxic regimen used to treat her.

There was no increase in peripheral neuropathy.

There were no grade 3, 4 or 5 WHO toxicity events.

The only toxicity was an increase in agitation in two subjects. This required an increase in the anti anxiety drug that they were already taking. It was not severe enough to stop therapy. Neuropsychiatric side effects have been described in children taking Montelukast for Asthma.

De-identified information about any unanticipated side effects to any subject will be given to patients on study and their treating

Statistical Analysis

Results of the patient's previous response to initial treatment were recorded before and after the addition of Montelukast. This will enable the use of a paired t-test to determine whether a significant benefit has been achieved. All patients will be included in analysis..

Assessment of response:

The multiple myeloma international working group response will be used in reporting results. It is intended that the trial be closed following the recruitment of 6patients and the results published irrespective of the outcome.

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Data Collection sheet. Initial Sheet MOM trial.

Eligibility checked

Consent material provided to patient.

Study design read, understood and signed by treating clinician.

Consent signed by patient/subject.

Patient Name

Date of Birth.

Age:

Gender:

Trial Number allocated: MOM

Trial Number: MOM

Initial Stage.

Response to last treatment. (has to be stable or progressive disease).

Current M protein: Date

Current Light Chain. Date

Bone Marrow % plasma cells (Date

Bone Marrow % cd38/138 +ve cells. (flow cytometry)

Bone Marrow % Cd 138 +ve plasma cells. Immunohistochemistry.

Protocol chosen. Standard, Less intense.

Haemoglobin

Neutrophil count

Platelet count.

Total protein Albumin

Urea

Creatinine.

egfr.

LFT: any abnormal Signature and Name and date.

Previous therapies. Please list and date.

Assessment sheet Just prior to Ninth dose. MOM trial Number.

Current M protein: Date

Current Light Chain. Date

Haemoglobin

Neutrophil count

Platelet count.

Total protein Albumin

Urea

Creatinine.

egfr.

LFT: any abnormal

Was there any toxicity that lead to a delay in dose?

Was there an increase in Neutrophil counts?

Was there an increase in neurological toxicity?

Was the patient hospitalised in the last 8 weeks and what was the reason.

Was there any unexpected side effects?

Please describe

Signature and Name and date.

Data Collection sheet. After 12 doses. MOM trial.

Patient Name

Date of Birth.

Age:

Gender:

Initial Stage.

Response to last treatment. (has to be stable or progressive disease).

Current M protein: Date

Current Light Chain. Date

Bone Marrow % plasma cells (aspirate) Date

Bone Marrow % cd38/138 +ve cells. (flow cytometry)

Bone Marrow % Cd 138 +ve plasma cells. Immunohistochemistry.

Protocol chosen. Standard, Less intense.

Haemoglobin

Neutrophil count

Platelet count.

Total protein Albumin

Urea

Creatinine.

egfr.

LFT: any abnormal

Signature and Name and date.

Mortality review 12 months. Or 2 years. MOM trial number.

Are they alive. Y/N What was the date of death

Did they die from disease or other cause?

Current M protein: Date

Current Light Chain. Date

Bone Marrow % plasma cells (aspirate) Date

Bone Marrow % cd38/138 +ve cells. (flow cytometry)

Bone Marrow % Cd 138 +ve plasma cells. Immunohistochemistry.

Haemoglobin

Neutrophil count

Platelet count.

Total protein Albumin

Urea

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egfr. LFT any abnormal

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