Thalidomide : An old wine in new bottle

MB Agarwal

Thalidomide was first introduced in West Germany in 1956 and the rest of Europe, Australia, Canada and South Africa in 1957. It’s release in the United States was delayed by Dr. Francis Kelcy of the US-FDA in view of concerns regarding the neuro-toxicity seen in animal studies. It was initially marketed as a sedative alternative to barbiturates in view of it’s rapid speed of onset, lack of hangover effect and apparent safety after overdose. In addition, thalidomide was detected to have a powerful anti-emetic effect and hence became popular amongst obstetrician as a preferred treatment of morning sickness for pregnant women.

However, soon after it’s release, there was a marked increase in cases of phocomelia (congenital limb foreshortening). In 1961, after reports linking this to in-utero thalidomide exposure, the drug was withdrawn leaving a legacy of about 10,000 affected children.

The drug was not entirely forgotten. Sheskin, an Israeli physician, administered some old supplies of thalidomide to his patient with mania and leprosy for inducing sleep. There was a dramatic and complete resolution of the patient’s cutaneous symptoms and Sheskin published this in 1965. This observation maintained the interest in thalidomide and it was soon obvious that the drug has important contribution in the treatment of erythema nodosum leprosum (ENL; a complication of the lepromatous form of leprosy). Subsequently, controlled clinical trials including a World Health Organisation coordinated randomized controlled trial, were carried out and thalidomide became the treatment of choice for moderate to severe ENL as it produced remarkable improvement in nearly all patients studied.

In 1991, thalidomide’s anti-tumour necrosis factor-α (TNF-α) activity was discovered and this virtually intensified the interest in the potential uses of this unique drug. It received US-FDA approval for the acute and maintenance therapy of ENL in June 1998 and currently is being evaluated or used on a compassionate-use basis in more than 30 conditions including dermatologic, infectious, autoimmune and malignant disorders.

PHARMACOKINETICS

Thalidomide (α-N-[phthalimido]glutarimide) is a derivative of glutamic acid. It is administered clinically as a 1:1 racemic mixture of its S and R isomers. It is well-absorbed after oral administration. Maximum plasma level of 1-4 µg/ml is reached within 2-4 hours. It is eliminated by spontaneous hydrolysis to multiple inactive metabolites. It has a half-life of approximately 5 hours. There is virtually no excretion via hepatic or renal pathways and the risk of drug interactions is negligible. It is possible that the anti-angiogenic effect of thalidomide in humans is due to a specific metabolite and not the parent compound. The structure of thalidomide is shown in Fig. 1.

Thalidomide has no suitable intravenous formulation as it has poor solubility in water and also because of it’s instability. Hence, the pharmacokinetic parameters have been determined by oral studies in animals and humans. It is evenly and widely distributed throughout most tissues and organs including the placenta. It’s metabolites are quickly excreted in the urine while unabsorbed portion is excreted unchanged in the feces.

EFFECTS OF THALIDOMIDE

Anti-tumour effects

Thalidomide has been tested in a variety of haematological and solid malignancies. It has shown remarkable efficacy in patients with advanced multiple myeloma. In fact, the use of thalidomide is arguably the most significant advance in the management of myeloma since the introduction of high dose Melfelan and autologous stem cell transplantation nearly 20 years ago. The exact basis for thalidomide’s anti-tumour activity is not well-understood. It may be related to its anti-angiogenic action, immunomodulatory effects, TNF-α-regulation, effect on cytokines and anti-adhesion effects.

Anti-angiogenesis

Many tumours require new vessel formation (angiogenesis) in order to support their continuous growth. There is strong evidence that neo-angiogenesis is an important aspect of pathogenesis of myeloma. Myeloma marrow shows increased microvascular density (MVD) and it’s MVD correlates with the clinical aggressiveness. Rajkumar SV et al demonstrated the prognostic implication of MVD. Myeloma cells secrete a variety of angiogenic factors. Thalidomide can inhibit angiogenesis induced by basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). In fact, thalidomide was first tested
in myeloma because of its known anti-angiogenic activity. It is also known that thalidomide-analogues impair VEGF-induced mitogen-activated protein kinase (MAPK) signalling pathways.26

There is emerging evidence suggesting that “angiocochemotherapy” (i.e. anti-angiogenic agent plus chemotherapy) is more cytotoxic than chemotherapy alone. General principles of anti-angiogenic therapy in the treatment of cancer are summarized in Table 1.

Table 1: Principles of anti-angiogenic therapy in neoplastic disorders

<table>
<thead>
<tr>
<th>Feature</th>
<th>Explanation</th>
</tr>
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<tbody>
<tr>
<td>Low toxicity</td>
<td>Acts on proliferating capillary endothelial cells. There is no myelosuppression</td>
</tr>
<tr>
<td>Prolong therapy needed</td>
<td>Unlike chemotherapy where short interrupted courses are given</td>
</tr>
<tr>
<td>Low risk of drug resistance</td>
<td>Both in animal trials and phase-2 human trials</td>
</tr>
<tr>
<td>Synergistic effect with chemotherapy</td>
<td>Angio-chemotherapy</td>
</tr>
</tbody>
</table>

Immunomodulatory properties

Thalidomide's immunomodulatory properties are complex and incompletely understood. Multiple mechanisms of action have been reported (Table 2).20 The best recognised action is its ability to inhibit the production of TNF-α.

1) TNF-α regulation

Researchers from the Rockefeller University and others have shown that thalidomide selectively inhibits TNF-α production in human monocytes, macrophages and neutrophils.27 In contrast with corticosteroids, thalidomide can do so without downregulating interleukin (IL)-1β or IL-2 production. Clinical efficacy of thalidomide in several corticosteroid-resistant immunological conditions has been noted. The anti-angiogenic effect of thalidomide may be related to inhibition of TNF-α as TNF-α has angiogenic effect. This, however, remains unconfirmed. Disorders where thalidomide is effective in this manner are depicted in Tables 3 and 4.

2) Effect on cytokines

Thalidomide can inhibit synthesis of IL-6, IL-12 and interferon-γ (IFN-γ).20 It can also switch cytokine production from Th1 to Th2 profile. It can augment production of IL-2, IL-4, IL-10, IL-12 and IFN-γ.20 Thus, thalidomide has bidirectional effect on some of the cytokines. These dichotomous results may be partly explained by its ability to act as a T-cell co-stimulant.

3) Effect on adhesion molecules

Thalidomide reduces expression of intracellular adhesion
molecule-1 and vascular cell adhesion molecule-1. (Fig. 2 for effects of thalidomide).

**ADVERSE EFFECTS**

Common adverse effects reported during treatment with thalidomide are summarized in Table 5. Common side-effects are sedation and constipation. The degree of sedation decreases with continued administration at a constant bedtime dosing. Fortunately, any ‘hang-over’ effect is minimal. Constipation is a significant problem with doses around 400 mg/d or more. Use of extra dietary-fiber and laxative helps.

The most serious adverse effect is teratogenicity.

<table>
<thead>
<tr>
<th>Table 4: Therapeutic uses of thalidomide: Malignant disorders</th>
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<tbody>
<tr>
<td><strong>A. Haematological malignancies</strong></td>
</tr>
<tr>
<td>* Multiple myeloma</td>
</tr>
<tr>
<td>* Myelodysplasia</td>
</tr>
<tr>
<td>* Myelofibrosis with myeloid metaplasia</td>
</tr>
<tr>
<td><strong>B. Solid tumours</strong></td>
</tr>
<tr>
<td>* Malignant glioma</td>
</tr>
<tr>
<td>* Kaposi’s sarcoma</td>
</tr>
<tr>
<td>* Prostatic carcinoma</td>
</tr>
<tr>
<td>* Colorectal carcinoma</td>
</tr>
<tr>
<td>* Renal cell carcinoma</td>
</tr>
<tr>
<td>* Carcinoma of breast</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5: Thalidomide: Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Teratogenicity</strong></td>
</tr>
<tr>
<td>* A single dose of 50 mg is adequate to produce serious defects</td>
</tr>
<tr>
<td><strong>Peripheral neuropathy</strong></td>
</tr>
<tr>
<td>* Predominantly sensory</td>
</tr>
<tr>
<td>* Axonal degeneration</td>
</tr>
<tr>
<td>* Occasionally permanent</td>
</tr>
<tr>
<td><strong>Somnolence</strong></td>
</tr>
<tr>
<td>* Virtually universal</td>
</tr>
<tr>
<td>* Administer at bedtime to reduce effect</td>
</tr>
<tr>
<td>* Tolerance develops</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
</tr>
<tr>
<td>* Occasionally severe</td>
</tr>
<tr>
<td>* Laxatives commonly needed</td>
</tr>
<tr>
<td><strong>Macular rash</strong></td>
</tr>
<tr>
<td>* Self-limiting on stopping treatment</td>
</tr>
<tr>
<td>* More common in HIV-positive patients</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
</tr>
<tr>
<td>* Rare</td>
</tr>
<tr>
<td>* More common in HIV-positive patients</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
</tr>
<tr>
<td>* Xerostomia</td>
</tr>
<tr>
<td>* Weight gain</td>
</tr>
<tr>
<td>* Oedema of face / limbs</td>
</tr>
<tr>
<td>* Decreased thyroid hormone production</td>
</tr>
<tr>
<td>* Hypotension</td>
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</tbody>
</table>

Phocomelia of the upper extremities is the most prominent congenital abnormality. Other birth-defects include congenital heart disease, spina bifida, facial palsies, abnormalities or absence of internal organs (kidney, spleen, gall bladder) and external features (ear, eye). 

Drug ingestion, even a single dose of 50 mg during days 35-50 of pregnancy produce the highest risk of embryopathy. Hence, the drug must not be used at any time during pregnancy. The recommended contraceptive methods must be used by both women and men of child-bearing potential.

The System for Thalidomide Education and Prescribing Safety (STEPS), implemented to ensure the safe
distribution of thalidomide, requires patient compliance with contraception guidelines and mandatory surveillance procedures. In addition, all who plan to prescribe/dispense thalidomide in US have to be registered with the program. With respect to myeloma, the overwhelming majority of affected women will be post-menopausal so that this risk is absent. Nevertheless, women of child bearing potential must exercise extreme precaution using two methods of contraception and regular pregnancy test. Men must be counselled to use barrier contraception if their partner is of child-bearing age as it is not known whether thalidomide is present in semen.

Another important toxicity is peripheral neuropathy. It is a symmetrical, painful sensory neuropathy. Electrophysiologic findings show axonal degeneration without demyelination. Common symptoms include numbness of the toes and the feet, cramps and weakness. Irreversible sensory loss can occur. Patient’s education for early detection of neuropathy and close monitoring including periodic electrophysiologic testing have been suggested. Patients must be taught regarding stoppage of drug whenever significant numbness or paraesthesiae develop. It is more common in older patients receiving high cumulative doses. Higher incidence seen in patients with HIV infection and malignancy could be partly related to chronic use of medications with neurotoxic potential. The aetiological assessment of neuropathy in myeloma patients becomes complex as the symptoms are of multifactorial origin i.e. paraprotein-related neuropathy, radicular or spinal cord compression, amyloidosis and vincristine effect.

Other known but uncommon complications include neutropenia, clinical hypothyroidism, bradycardia, cutaneous rashes and an occasionally serious skin reactions. Venous thromboembolism (VTE) has been noticed, especially in patients with malignancy. This has been discussed later (vide-infra).

**Thalidomide Derivatives**

Over the last few years, scientists have developed structural analogues that possess thalidomide’s immunomodulatory properties without associated side-effects. Several such compounds have been developed. They are up to 50,000-fold more potent than thalidomide in inhibiting TNF-α on a molar basis. These analogues, depending upon their biological effects, can be broadly split into two main groups.

The first group includes immunomodulatory derivatives (IMiDs). They strongly inhibit TNF-α along with IL-1β, IL-6 and IL-12 and augment IL-10 production. They are also potent co-stimulators of T-cells and dramatically increase T-cell proliferation. They do not inhibit phosphodiesterase-4.

The second group includes several selective cytokine-inhibitory drugs. These are also potent inhibitors of TNF-α. However, they have considerably less effect on other inflammatory cytokines. They have no effect on T-cell activation and even cause slight inhibition of T-cell proliferation. They also inhibit phosphodiesterase-4.

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**Clinical Applications**

**Leprosy**

Erythema nodosum leprosum (ENL) is an acute vasculitis seen in patients with lepromatous leprosy after anti-lepromatous treatment. It is characterized by a painful, ulcerative, nodular rash with systemic symptoms such as fever, arthralgia, neuritis and glomerulonephritis. It is both a cell-mediated immune response as well as an immune complex-mediated disease. Patients have raised INF-γ, TNF-α and IL-12. Thalidomide’s effectiveness is due to it’s anti-cytokine properties. After therapy, there is marked reduction in TNF-α along with downregulation of intracellular adhesion molecule-1. Many patients require a low dose maintenance therapy.

**Aphthous ulcers**

Resistant oral aphthous ulceration primary or secondary to Behçet’s disease and HIV infection respond to thalidomide in over 50-60% of patients. However, the ulcers often recur after cessation of therapy, necessitating recurrent courses of treatment.

**Crohn’s disease**

After the discovery of central role of TNF-α in the pathogenesis of Crohn’s disease, thalidomide was used and shown to be effective in steroid-resistant cases of this disorder. Thalidomide has also been used as maintenance therapy after inducing remission with infliximab.

**Wasting and cachexia**

Thalidomide has been shown to retard or reverse the weight loss associated with a number of conditions i.e. HIV infection, active pulmonary tuberculosis and advanced malignancies. Cachexia, in these disorders, is mediated through a Th1 immune response with increased production of TNF-α, IL-1β and IL-6, all of which are reversed by thalidomide.

**Rheumatological disorders**

Many autoimmune disorders related to rheumatology have been shown to respond to thalidomide, however, these have been small case-series and currently, there is not enough reliable evidence to support this use.

**Graft vs host disease (GvHD)**

Encouraging results have been shown using thalidomide in patients with refractory chronic GvHD (40-60% response). However, the benefit achieved by adding thalidomide over and above that achieved by conventional immunosuppressive therapy is small.

**Dermatological conditions**

Thalidomide is an effective anti-pruritic agent. It has been used for treating prurigo nodularis, uraemic pruritus, porphyria cutanea tarda, disoid lupus, actinic prurigo and pyoderma gangrenosum.

**Solid organ malignancies**

Patients with Kaposi’s sarcoma, renal cell carcinoma, high grade glioma, advanced melanoma and advanced breast
cancer have all been treated with thalidomide with variable response. Recently, however, there are several reports indicating high incidence of thromboembolic disease in patients with advanced cancer treated with thalidomide (vide infra). Therefore, as a single drug, presently, thalidomide has not been widely recommended for treatment of solid organ malignancies. It’s potential in combination therapy, however, is currently under investigation.

Haematological malignancies

There has been considerable interest in the use of thalidomide in haematological malignancies such as multiple myeloma, other plasma cell dyscrasias, myelodysplastic syndrome (low risk), chronic myeloproliferative disorders especially myelofibrosis with myeloid metaplasia and even in acute leukaemia. This is in view of thalidomide’s immunomodulatory and anti-angiogenic properties together with convincing documentation that angiogenesis is an important mechanism in progression of haematological malignancies.

Multiple myeloma

Relapsed / refractory cases

Barlogie et al initiated clinical studies with thalidomide in refractory / relapsed multiple myeloma. Their results, published in 1999 by Singhal et al, demonstrated an overall response rate of 32% in 84 patients with relapsed / refractory myeloma. Considering that 90% of patients in this study had failed autologous stem cell transplantation, these results were very impressive. Barlogie et al updated these results in 169 patients and also identified the prognostic factors in a phase-2 study in 2001. They concluded that thalidomide represents the first new class of active agents in the treatment of multiple myeloma since the introduction of melphelan and glucocorticoids more than three decades ago. The possible anti-tumour mechanisms of thalidomide in multiple myeloma include: 1) A direct effect on myeloma and/or bone marrow stromal cells; 2) Modulation of myeloma - stromal cell adhesion; 3) Suppression of myeloma cell - sustaining cytokines; 4) Anti-angiogenic effects (on VEGF and bFGF); 5) Immunomodulation with enhanced secretion of interferon-γ and IL-2; and 6) Synergistic apoptotic signaling of thalidomide and dexamethasone.

The prognostic factors for thalidomide efficacy included low plasma cell labeling index (PCLI below 0.5%), low serum β-2 microglobulin i.e.< 3 mg/L and normal cytogenetics. Two-year event-free and overall survival rates were 20% ± 6% and 48% ± 6%, respectively. A dose-response effect was also shown as the response rates were higher and survival was longer in patients receiving over 42 gm of thalidomide within 3 months.

The activity of thalidomide in relapsed / refractory myeloma has since been confirmed by numerous studies worldwide. These studies indicate a median response duration of one year. Approximately, 20% of patients are free of progression at 2 years. Thalidomide, hence, is now considered as a standard therapy for relapsed / refractory myeloma.

Early-stage myeloma

Thalidomide has also been tested in early-stage myeloma patients. Three studies in untreated patients with indolent, smoldering or early myeloma indicated the response rate of approximately 38-40%. Prior to thalidomide, the standard approach in treating these patients has been observation without therapy. Randomized trials are underway to determine whether low dose thalidomide can delay the progression of such patients to active symptomatic disease.

Thalidomide plus dexamethasone

A critical question is whether it is beneficial to continue thalidomide with other active anti-myeloma agents. Weber et al observed responses in 24 (52%) of 47 patients with resistant myeloma using a combination of thalidomide and dexamethasone. Many patients (46%) in this trial had previously failed dexamethasone or thalidomide as single agent, suggesting a synergistic effect of combined therapy. Demopoulos et al have also shown similar results. Rajkumar et al have shown their results in untreated cases of myeloma using combination of thalidomide and dexamethasone. Preliminary results from a Mayo Clinic study using this combination as initial therapy for untreated myeloma indicated a response rate of over 75%. Laboratory studies also support the presence of synergistic interactions between thalidomide and dexamethasone. A major potential advantage of this regimen (in newly diagnosed cases) is that it obviates the need for a long-term central venous catheter with its associated risks of infection and line-related thrombosis as the observed partial remission rates are comparable to VAD (vincristine, adriamycin, dexamethasone) - like regimens.

Thalidomide plus chemotherapy

Kropff et al studied hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (hyper-CDT) in primary refractory or relapsed myeloma. Moehler et al, in another study, treated 42 patients with advanced myeloma with T-CED (thalidomide, cyclophosphamide, etoposide and dexamethasone) with 78% partial remission. Barlogie et al as well as Tricot et al from University of Arkansas have studied the largest number of previously treated patients and concluded that DT-PACE (dexamethasone and thalidomide with infused cisplatin, doxorubicin, cyclophosphamide and etoposide) is an excellent induction regimen. These patients, however, needed subsequent high dose therapy for ‘durable’ disease control.

These impressive results have encouraged studies examining combination of thalidomide and conventional chemotherapy in newly diagnosed patients of myeloma. The results are awaited with interest.

Myelodysplastic syndrome

Thalidomide has considerable efficacy in the treatment of patients with low risk myelodysplastic syndrome (MDS). Role of increased marrow angiogenesis in MDS has been shown. Similarly, autoreactive T-cells appear to contribute to the bone marrow failure in MDS. Strupp et al studied...
the efficacy of thalidomide in 34 patients with MDS with a median dose of 400 mg/d. A therapeutic benefit was achieved in 19/34 (56%) patients. In fact, nine patients achieved partial haematological remissions with absolute neutrophil count >1500/cmm, Hb >11 g/dl and platelet count >100,000/cmm. There are other recent reports regarding thalidomide treatment in myelodysplastic syndromes as well. It is hoped that future studies would contribute further to the exact role of thalidomide in the management of MDS including in the understanding of its mechanism of action.

**Myelofibrosis with myeloid metaplasia**

Thalidomide, at conventional doses (>100 mg/d), has been evaluated in myelofibrosis with myeloid metaplasia (MMM). It produces approximately a 20% response rate in anaemia. In all patients with MMM for 3 months and showed good tolerance in all patients with an objective clinical response in 13 (62% patients), all related to improvements in anaemia. The responses observed were mostly durable after discontinuation of prednisolone. They concluded that thalidomide-prednisolone is a well-tolerated and promising new drug regimen for treating cytopenias in patients with MMM.

**Newer Toxicity : Venous Thromboembolism**

Although teratogenicity and neuropathy are considered as the most serious potential adverse events related to thalidomide therapy, venous thromboembolism (VTE) has emerged as the single most important complication of thalidomide in the setting of malignancy especially multiple myeloma. VTE was noticed in less than 5% of advanced myeloma patients taking thalidomide as a single agent. However, an unexpectedly high risk of VTE was observed when thalidomide was combined with chemotherapy for newly diagnosed patients with myeloma. Rajkumar et al reported an incidence of 10% using thalidomide and dexamethasone as initial therapy. Osman et al found it in 4/15 patients on TAD (thalidomide, adriamycin, dexamethasone) regimen given as an induction therapy for newly diagnosed myeloma patients. Zangari et al from the University of Arkansas reported an incidence of 28% in the thalidomide plus chemotherapy arm v/s 4% in chemotherapy (i.e. no thalidomide) arm. All these episodes occurred in the first three cycles of therapy i.e. when the tumour bulk was maximum. No identifiable prothrombotic laboratory abnormality has been found to be predictive of VTE in this group of patients. Addition of adriamycin invariably resulted in an increased VTE rate. Bennet et al reported varying rates of VTE with thalidomide alone (4.6%), in combination with dexamethasone (15%) and with chemotherapy (30.9%) in patients with a variety of cancers. It may be concluded that use of thalidomide concurrently with chemotherapy in patients with newly diagnosed myeloma carries a significant risk of VTE. The major risk occurs early on in treatment when the tumour load is maximal. Therefore, a combination of thalidomide, chemotherapy and large tumour bulk is particularly prothrombotic in myeloma. Myeloma patients often have multiple contributory risk factors for VTE such as immobility, dehydration, increased plasma viscosity, intercurrent infections and acquired protein-C resistance (APC-R). It has been suggested that all such patients are candidates for appropriate VTE prophylaxis. Low-dose warfarin prophylaxis was, in fact, found to be effective by Barlogie’s group in reducing the VTE rate. Others are not convinced.

**Conclusions And Future Prospects**

Thalidomide, therefore, has significant activity, both alone and in combination with dexamethasone or other chemotherapeutic agents, in patients with de novo as well as advanced myeloma. Although, the optimal dose remains uncertain, the majority of patients will respond to a dose of 200-400 mg or even less. Most patients are intolerant to a dose greater than 600 mg. Role of thalidomide in maintenance therapy is under study.

It has a significant side-effect profile but is tolerated by the majority of patients. Peripheral neuropathy has to be remembered. Clinical vigilance is essential to avoid serious neurotoxicity as routine serial nerve conduction studies are not practical in myeloma patients.

The incidence of VTE varies in different patient groups and with different protocols. Prophylactic low dose anticoagulation therapy has been suggested and is useful, although, no firm recommendations can be made at this stage. Thus thalidomide, a biological agent, is a huge step forward and a very major advance in the clinical management of myeloma. In fact, its success in myeloma has opened a new field for searching alternative ‘biological’ agents having great potential in the treatment of myeloma and allied conditions. These include proteosome inhibitors, bcl-2 antisense, other angiogenesis inhibitors and farnesyl transferase inhibitors.

It is extremely important that thalidomide itself and all these other new agents are tested appropriately in well-planned prospective clinical trials.

**References**

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Announcement

Indian Society of Critical Care Medicine, Jaipur Chapter

Rungta Hospital, Malviya Nagar, Jaipur - 302 017

National Workshop on Mechanical Ventilation will be held on 27th July, 2003.

Registration Details : Only 50 seats are available on the first come first serve basis. The registration fee is Rs. 750-. For those who will be attending the FCCS course, the registration fee would be Rs. 500/-. Details of Payment : Demand Draft Rs. 750.00/500.00 towards registration for the National Workshop on Mechanical Ventilation.

For further details contact : Dr. Narendra Rungta, Hon. Secretary, Jaipur Chapter of Indian Society of Critical Care Medicine, Rungta Hospital, Malviya Nagar, Jaipur - 302 017, India.

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