at the population level. However, the impressive reduction in neonatal mortality in those who received postnatal visits shows a promising potential for the programme if coverage can be improved.

COMMENT

India contributes to 25% of the global neonatal deaths[1] and, for a developing country like ours, community and family-level interventions are crucial to reduce the burden of neonatal mortality. In settings where health systems are weak, early success in averting neonatal deaths is possible only through outreach, family–community care including health education to improve home-care practices and healthcare seeking, as was emphasized in the *Lancet* neonatal survival series.[2] This programme, which is a partnership between an international NGO and the Government of India, is a step towards strengthening the family–community level of care.

This study with a robust design and statistical methods tries to fill a gap in population-level data regarding the actual exposure of the families to large, community-based programmes and the behavioural change resulting from them. The uniqueness of this programme lies in the fact that it used the existing government infrastructure and personnel to deliver antenatal and postnatal services and change health-seeking behaviour. The programme used interventions already proven to reduce neonatal mortality in community-based efficacy trials. These trials were conducted in highly controlled programme areas and used specially designated personnel to deliver the services unlike the current programme which was set up in a 'real-life situation'.

Though some of the maternal behaviours improved in the intervention district, this did not translate into better neonatal survival. This was predominantly due to inadequate coverage by community-level workers. Only one-third of all mothers had at least 1 antenatal and postnatal visit at the end-line survey even in the intervention district and <25% of neonates received a home visit in the crucial initial 3 days after birth. Other trials such as the Gadchiroli field trial, which was conducted in a controlled environment with high coverage, could demonstrate a significant decrease in neonatal mortality even with home-based care.[3] Large scale programmes such as the Integrated Management of Childhood Illness (IMCI) have also shown varied effectiveness in different countries largely due to variations in implementation.[4] Another possible reason for the lack of reduction in neonatal mortality could be that postnatal interventions in this programme did not contain some of the cost-effective interventions of proven efficacy such as pneumonia case management. According to the *Lancet* neonatal survival series, the predicted reduction in neonatal mortality with this intervention is 27%.[2]

Some of the results of the study should be interpreted cautiously. A post hoc analysis of the pooled data of both intervention and comparison districts revealed that postnatal visit alone reduced the neonatal mortality with or without an antenatal visit and this benefit persisted after excluding deaths that occurred on the day of birth. As the comparison district was out of the INHP, the content of antenatal counselling and type of antenatal care might have been significantly inferior in this area and could have adversely affected the importance of the antenatal visits in the pooled data. As rural mothers who had given birth in the preceding 2 years were interviewed, the reliability of some items such as breastfeeding in the first hour, thermal care for first 6 hours and postnatal visit on the day of birth remains questionable due to recall bias, and pooling the data may increase this bias.

In conclusion, though community-based, cost-effective interventions to reduce neonatal mortality are known, this study highlights that implementation of such interventions on a large scale within the existing health systems is not easy. There is a need to conduct operational research on strategies for better coverage and implementation such as simple tools for administration, focused content, better supervision and training for field assessment skills.[5]

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Further progress in the treatment of multiple myeloma?

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St Petersburg, Russia; Myeloma Study Group, Belgian Hematological Society, Brussels; People's Hospital, Peking University, Beijing; Dana–Farber Cancer Institute, Boston; Millennium Pharmaceuticals, Cambridge, MA; and Johnson and Johnson, Raritan, NJ, and Beerse, Belgium.) Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008;**359:**906–17.

SUMMARY

The management of multiple myeloma (MM) has evolved over the past 2 decades from an incurable disease to a chronic illness. Recently, 2 new drugs—lenalidomide (a thalidomide analogue) and bortezomib (a proteosome inhibitor)—have been used for the treatment of MM. Treatment with bortezomib, dexamethasone and/or doxorubicin in relapsed/refractory MM is associated with a complete response rate of 30%.[1] Based on these results, bortezomib has been approved for the initial treatment of this disease.

This phase III trial included patients with newly diagnosed symptomatic, measurable MM who were not suitable for high dose chemotherapy and stem cell transplantation (SCT) because of age (>65 years) or coexisting conditions. It enrolled 682 patients (151 centres, 22 countries) and randomly assigned them to receive either bortezomib, melphalan and prednisone (*n*=344; bortezomib group) or melphalan and prednisone (*n*=338; control group). The baseline demographic and disease characteristics were comparable in the two groups. Patients received nine 6-weekly cycles of melphalan (9 mg/m^2) and prednisone (60 mg/m^2) on days 1–4 alone or along with bortezomib (1.3 mg/m^2) on 8 days each during cycles 1–4 and on 4 days each during cycles 5–9.

The primary end-point of the study was time to disease progression. Secondary end-points included rate of complete response, duration of response, time to subsequent MM therapy and overall survival. Complete and partial responses were defined according to the European Bone Marrow Transplantation group (EBMT) criteria.[2] Briefly, complete response was defined as absence of M protein in serum and urine confirmed in 2 samples by immunofixation, and <5% marrow plasma cells. Partial response was defined as reduction in the serum level of M protein of at least 50% and a reduction in the urine of at least 90%. Near complete response (very good partial response) was defined as complete response without confirmation of a decrease in marrow plasma cells to <5% by bone marrow biopsy, confirmation of the disappearance of M protein in serum or urine by repeat immunofixation, or both. Progressive disease was defined as any of the following: (i) absolute increase of >500 mg/dl of serum M protein compared with the nadir value; (ii) absolute increase of >200 mg of urinary M protein in 24 hours; (iii) new bone lesion or plasmacytoma; (iv) increase in the size of such lesions; or (v) development of hypercalcaemia (serum calcium level >11.5 mg/dl [2.9 mmol/L]). The data were analysed for time to progression, time to subsequent MM therapy and overall survival. For time to progression analyses, data from patients in whom there was no disease progression were censored at last assessment or at start of subsequent therapy.

The response was evaluated in 337 patients in the bortezomib group and 331 in the control group. The partial and complete response rates were 71% and 30% in the bortezomib group, and 35% and 4% in the control group, respectively (p<0.001). The median duration of response was 19.9 months in the bortezomib group compared with 13.1 months in the control group. The median time to progression was 24 months in the bortezomib group and 16.6 months in the controls (hazard ratio [HR] bortezomib group: 0.48; p<0.001). This benefit in time to progression was independent of risk factors such as age, sex, race, baseline b2 microglobulin level, albumin level, geographical region, international staging (ISS)[3] or creatinine clearance. The median time to subsequent therapy and the associated treatment-free interval were significantly longer in the bortezomib group than the control group (p<0.001). At a median follow up of 16.3 months, 45 patients (13%) in the bortezomib group and 76 (22%) in the control group had died (HR bortezomib group: 0.61; p=0.008). The median survival was not reached in either group. The estimated overall survival at 30 months in the bortezomib group was 83% compared with 67% in the control group.

COMMENT

The use of thalidomide, lenalidomide and bortezomib has led to a paradigm shift in the management of MM over the past decade resulting in better outcomes.[1] Melphalan, prednisolone and thalidomide are currently used as the standard of care in elderly, newly diagnosed patients with MM.[4] To further improve the outcome, a combination of these drugs with lenalidomide or bortezomib (these have marked activity in relapsed/refractory MM) is being investigated.[5–9] Lenalidomide, an analogue of thalidomide, has potent antimyeloma activity. It induces apoptosis, decreases the binding of myeloma cells to stromal cells in the bone marrow, inhibits angiogenesis and promotes cytotoxicity mediated by natural killer cells. Unlike thalidomide, sedation, constipation and neuropathy do nor occur but myelosuppression (neutropenia and thrombocytopenia) occur in less than one-third of patients. Bortezomib is a potent, selective and reversible inhibitor of the small molecule 26S proteosome; a large intracellular ATP-dependent protease responsible for protein catabolism in all eukaryotic cells. The proteosome plays a key role in the degradation of ubiquitinated proteins, which in turn have important functions in controlling tumour cell growth and survival.

The combination of bortezomib with melphalan and prednisone, used in newly diagnosed elderly patients who were not candidates for high dose therapy, in phase I/II trials provides a response rate of 89%; 32% complete response and 11% near complete response.[6] The response rate was higher and 16-month progression-free survival, event-free survival, and overall survival rates were also significantly better with bortezomib, melphalan and prednisone than with melphalan and prednisone.[8]

This phase III study has also demonstrated that bortezomib, melphalan and prednisone in elderly patients as first-line therapy is better than melphalan and prednisone in terms of higher response rates, time to progression, treatment-free interval and overall survival. The median number of cycles administered was comparable and median dose intensities for melphalan and prednisone were the same in both the groups. There were no significant differences in toxicity in the two groups. However, peripheral neuropathy (all grades), gastrointestinal symptoms and the incidence of herpes zoster were more in the bortezomib group. The frequency of peripheral neuropathy was similar to previous studies[5–7] and was reversible in most cases.

Apart from bortezomib, thalidomide and lenalidomide have been shown to be useful in newly diagnosed, elderly patients. The French Group trial (IFM 99-06 trial) showed that a combination of melphalan, prednisolone and thalidomide was associated with a significantly better overall survival than melphalan and prednisolone (HR 0.59, 95% CI 0.46–0.81, p=0.0006).[8] The report from the GIMEMA—Italian Multiple Myeloma Network showed that a combination of lenalidomide, melphalan and prednisone in newly diagnosed elderly patients achieved an 81% partial response rate, 47.6% good partial response rate and 23.8% complete (immunofixation-negative) response rate. In all patients, the 1-year event-free and overall survival rates were 92% and 100%, respectively.[8] In view of the increased activity,

a combination of bortezomib and lenalidomide along with low dose dexamethasone is being studied in the Southwest Oncology Group trial[9] and results in a higher complete response rate (>30%) with a 2-year estimated survival >80% but with a short follow up.

Whether to choose lenalidomide, melphalan and dexamethasone or bortezomib, melphalan and dexamethasone or bortezomib, lenalidomide and dexamethasone is not clear. Future studies need to address this and the toxicity profile, cost analysis, quality of life and long term follow up data will help choose one combination over the other.[11]

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