

Non-Hodgkin's lymphoma: Is India ready to incorporate recent advances in day to day practice?

ABSTRACT

Background: Non Hodgkin's Lymphoma (NHL) cure rates are increasing and morbidities are decreasing, with more active pharmacological agents and technological advancements. In spite of this, India is still battling with the prejudices of an economically and educationally impoverished patient base.

Methods and Results: We analyzed NHL cases from 2000 to 2006 using data from case sheets. Of 303 cases, only 100 patients had complete workup and received some form of treatment. For 203 patients, reasons for non-compliance were: financial constraint (119), distance from center (38), inability of physician to provide guarantees of cure (13), poor prognosis/fear of recurrence (28), preferences for alternate medicine (5). Most common investigations that could not be afforded for staging were whole body CT scans and bone marrow aspiration and biopsy. Thirteen patients were in stage III and 53 in Stage IV. The most common regimen was CHOP (Cyclophosphamide, Adriamycin, Vincristine, Prednisolone). Forty-five patients did not complete six courses of CHOP and 35 patients had significant delay. Reasons for delay were intermittent availability of cash (35), intolerable toxicities (30), absence of supportive care (21), given-up attitudes (17). Eighty-three patients suffered Grade III/IV debilitating toxicities. Overall survival at five years was 50%.

Conclusions: NHL in India is no different from the developed world. However, there are disparities in survivorship and outcomes, due to un-affordability and attitudes of the patients. Therefore, we suggest the development of Community Health Insurance Schemes (CHIs), with the hospital as the nodal center to address the above mentioned issues.

KEY WORDS: CHOP, community health insurance, international classification of disease for oncology, non-Hodgkin's lymphoma

INTRODUCTION

It is common knowledge that a large percentage of patients with Non Hodgkin's Lymphoma (NHL) are curable with the combination of chemotherapy and radiation. The cure rates are increasing and long term morbidities decreasing, with the advent of more active pharmacological agents and technological advancements in radiation therapy equipment.^[1-4]

NHL has slowly grown from a rare cancer to the fifth most common cancer (incidence of 19.1 per 100,000 in USA) in the world.^[5] In India its incidence is on the upsurge with the current figure standing at 5.1 per 100,000 in urban registries.^[6]

In spite of the numerous advancements in the diagnosis (FDG-PET and Molecular markers of prognosis) and treatment (monoclonal antibodies, bone marrow transplantation and conformal radiation techniques),^[7,8] we, in India, are still battling the prejudices of an economically and educationally impoverished patient base. Even as the developed world is talking of improving

outcomes in its geriatric population we are still struggling to improve the quality of life of our young and productive population.^[9]

In light of the above stated advancements we decided to analyze our experiences with NHL and tried to answer the question - Are we ready to incorporate these improvements in our day-to-day practice?

MATERIALS AND METHODS

Cases of Non Hodgkin's Lymphoma registered at our institute between the years 2000 to 2006 were analyzed. The International Classification of Disease for Oncology (ICD-O) was followed to classify the cases as per histo-pathological findings. ICD-O numerical stages 959, 967, 968, 969, 970, 971, 972 and 973 were considered. Sub-types were classified strictly in accordance with this classification. Clinical stage was defined according to the Ann Arbor classification. Details about treatment were obtained under the following parameters-regimen adopted, date of starting chemotherapy, date of completion, number of

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DOI: 10.4103/0973-
1482.63571

cycles taken, toxicities due to treatment, delay(s) in treatment, cause(s) for delay and application of Involved Field Radio Therapy (IFRT). Follow up of patients was analyzed as per the records and tabulated under date of recurrence, date of last follow-up, status during last follow-up, duration of follow-up.

RESULTS

Between January 2000 and 2006, 303 cases of Non-Hodgkin’s Lymphoma were registered at our center. Fifty five (55) patients (18.1%) were excluded as the patients did not come after the first visit and the work up was not complete. Hence, 248 patients (81.8%) were assessed. Amongst these patients, 164 (66.1%) were male, and 84 (33.9%) female. The median age of our study population was 55.5 years (interquartile range 41-67 years). Seventy (70) (28.2%) patients did not have sub typing of NHL [Figure 1]. Out of the remaining 178 (71.7%), the most common histopathology was Diffuse Large B-Cell Lymphoma ICD 9680/3 in 67 patients (37.6%). Twenty (20) patients (11.2%) were Mixed Small and Large Cell Diffuse Lymphoma ICD 9675/3, and the remaining 91 patients (51.2%) were of other histopathologic subtype as shown in Figure 2.

Of these 178 patients, only 100 patients (56.1%) had complete workup and received some form of treatment. The remaining 78 patients (43.8%) did not have complete staging information and did not receive any treatment. For the 203 patients, the reasons for incomplete staging evaluation or refusal of any kind of treatment were financial constraints (119), coming from far-off places (38), inability of the physician to provide guarantees for a high chance of cure despite taking such expensive treatment (13), poor prognosis in advanced disease/fear of recurrence (28), preferences for alternate medicine like Ayurveda, Homeopathy, Unani and Siddi-5 [Figure 3]. The most common investigations that could not be afforded for staging were whole body CT scans (96%) and bone marrow aspiration and biopsy (44%).

Stage I and II Lymphomas were found in 34 patients (34%), 13 patients (13%) were of stage III and the remaining 53 patients

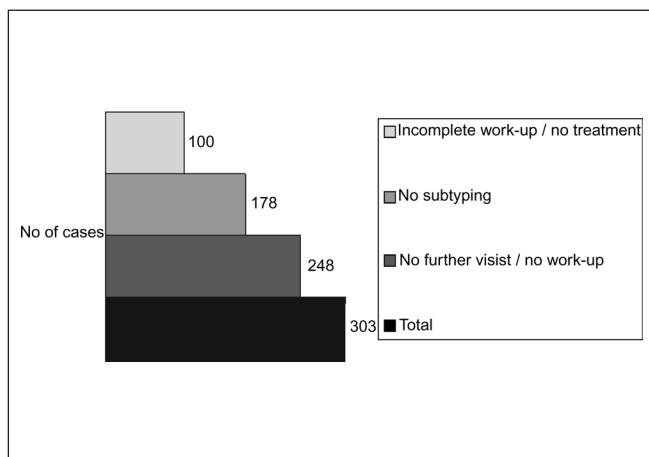


Figure 1: Number of dropouts at successive stages of therapy

(53%) were in Stage IV. Extra nodal presentation was found in 24 patients (24%) of the analyzable population of 100 patients. Thirty-one patients (31%) out of 100 presented with B-symptoms.

The most common regimen adopted was CHOP/CEOP (79%). Chlorambucil-based regimen was offered to seven patients (7%) with low-grade advanced-stage lymphomas. Other regimens were offered were COP, IMVP-16 (for patients with cardiac dysfunction), and PRO-MACE CYTABOM (for highly aggressive lymphomas). Out of 100 patients, 45 (45%) did not complete six courses of CHOP and 35 had significant chemotherapy delay. Only 20 patients (20%) completed the chemotherapy in time, i.e. within two weeks of scheduled completion. Median delay of 61 days (Q75-Q25 = 94-29) was observed. Reasons for delay were financial constraints/intermittent availability of cash for treatment in daily-wage workers -35, stoppage due to intolerable toxicities (either by patients or physicians)-30, inability to take supportive care (like G-CSF)-21, given-up attitudes of patients and their family members-17 [Figure 4].

Eighty-three patients (83%) suffered from some form of Grade III/IV debilitating toxicities. Most common toxicities were gastrointestinal toxicities (nausea, vomiting, constipation, abdominal pain, diarrhea, dyspepsia and organomegaly)-52 patients (52%). General toxicities (fatigue, chill and pedal edema) were observed in 51 patients (51%). Hematological toxicities (neutropenia, thrombocytopenia, and anemia) were observed in 47 patients (47%). Central Nervous System toxicities (peripheral neuropathy, headache, syncope and neuro-psychiatric symptoms) were observed in 19 patients (19%). Cardiovascular System showed toxicities in 11 patients (11%) - (Left ventricular dysfunction, arrhythmias and hypotension). Seventy-three patients (73%) had multiple toxicities [Figure 5].

Involved field radiation treatment was given to 13 (13%) of the 100 patients.

The median duration of follow-up for our study group was 11.2 months (Q75-Q25 = 38.06-3.55) from the start of treatment. A survival analysis of 100 patients who received some form of

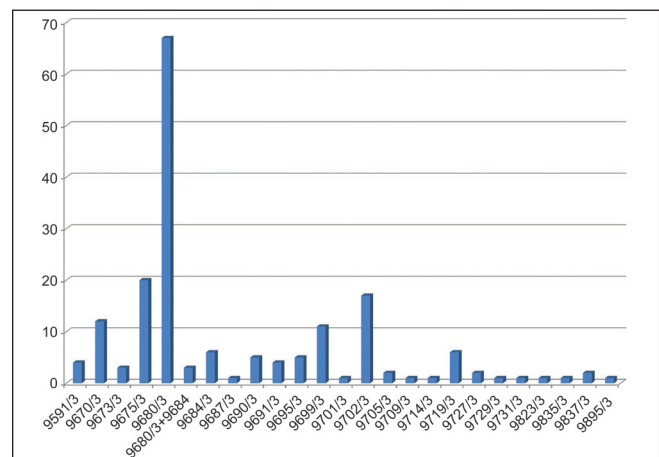


Figure 2: Classification of histopathological findings as per ICD-O

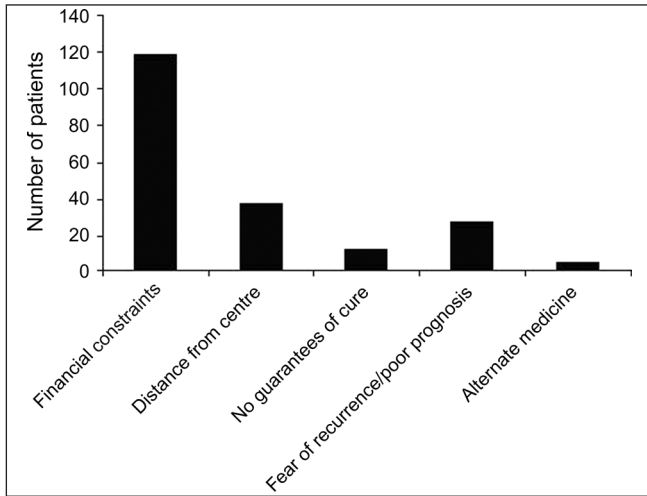


Figure 3: Reasons for dropouts at successive stages of therapy

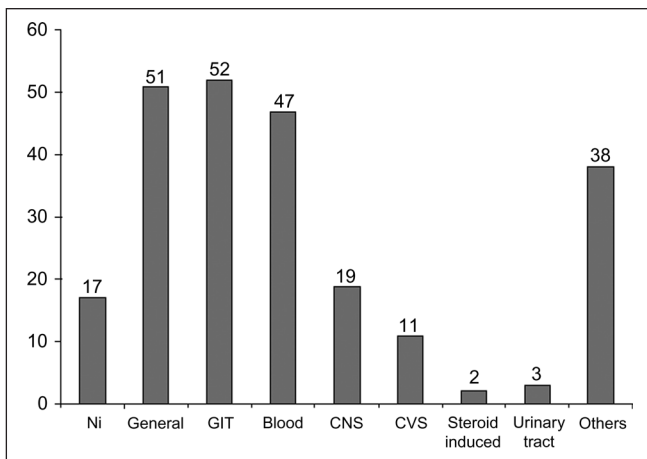


Figure 5: System-wise toxicities observed

treatment shows that overall survival at five years was 50% and the mean duration of survival was 63.65 months [S.E = 5.92, 95% CI 51.95-75.15] [Figure 6].

DISCUSSION

Our center, based in rural part of the state, caters to a patient population from urban, semi-urban and rural areas of three neighboring states. These patients come to us from a radius of 500 kilometers. The cancer center is equipped with modern radiation and medical oncology treatment facilities and social work support. The cost of treatment is moderate, to cater to all classes of people. The hospital has a Trust through which patients receive funds for treatment but it is often not sufficient to take care of the rising costs of health care.

NHL commonly presents in the sixth to seventh decade of life (median age of our population was 55.5 years) with a male preponderance (50-75%) for various histologies (66.1% of our patients were males). Stage I and II at presentation is seen in 40% (34% in our study) while stage IV is seen in 50% patients (53% in our study). B-symptoms and extra nodal presentations

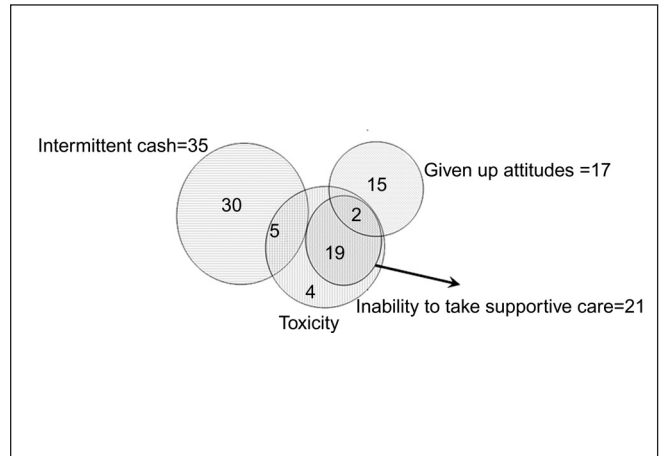


Figure 4: Reasons for incomplete / delayed completion of treatment

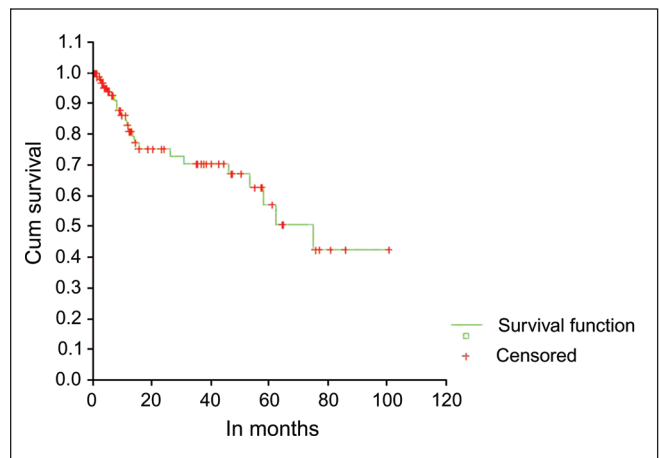


Figure 6: Survival analysis

are seen in about 1/3 of the patients (31% and 24% in our study respectively).^[5] This data establishes the fact that NHL in India is no different from the developed world. Thus one would expect similar survivorship and outcomes between the western world and India.

As per literature, five-year survival rates for early stage (I and II) and advanced stage (III and IV) are 77-82% and about 50-60% respectively. Grade IV toxicity is expected to occur in about 30-40% patients.^[1-4]

Survival can be further improved by about 10-20% with strategies like use of Rituximab (anti-CD20 monoclonal antibody) and dose intensification of the CHOP regimen.^[1,9] However, the second strategy requires the incorporation of G-CSF in the regimen. The use of radiotherapy in early stage disease provides a gain of 16% over chemotherapy alone and is of paramount importance for loco-regional control of disease. The use of PET scanning not only helps in predicting a durable response in complete responders but also is a useful modality for assessing residual disease. These patients may benefit from additional therapy in the form of radiotherapy or autologous bone marrow transplant or the addition of radio-immunotherapy.

The above facts and figure seem to present a pretty rosy picture. However, it comes at a cost.

In our study, 70 of 248 patients (28.22%) did not have sub typing i.e. no immunohistochemistry. Seventy-eight (78) out of remaining 178 (43.83%) did not complete staging work up and dropped out before start of treatment. Out of the 100 patients, 45 (45%) dropped out before the completion of therapy. Thus 77.8% of patients at our center drop out of the minimum basic therapy at some point in time or other. Approximately 57% patients drop out even before commencement of therapy. Moreover, consolidation radiation therapy was administered to miniscule 13% of our eligible population. The most common investigation, which was not available for the non-staged patients, was CT scan which is relatively expensive. The most commonly cited reason for dropping out were a) financial constraints, b) inability of the physician to provide 100% cure rates in spite of administering such expensive treatment (cost of one course of CHOP is Rs. 3500 at our center and radiation on LINAC about Rs 15,000), c) resorting to alternative medicines like Ayurveda for treatment.

Eighty-three per cent (83%) of our patients suffered from toxicities during treatment. A large number of these patients suffered from multiple toxicities. Due to this chemotherapy was often delayed (median delay 61 days). It also added to the drop out rate. The reasons for these increased toxicities are mainly a) financial constraints to afford supportive care, b) long distance travel to reach the center in case of emergencies. The (a) give-up attitudes of patient and family members, (b) intermittent availability of cash in daily wagers and (c) self stoppages during periods of toxicity led to the large amount of delay and the small percentage (20 of 100) patients completing therapy on time.

Even though we have used CHOP for most of our patients it is of note that in spite of FDA approval of Rituximab in 1997 we have not been able to administer this drug for any of our patients till 2006. PET Scans have also not been used in our patients. This is due to the high cost and sparse availability of Rituximab and PET. The median duration of follow-up is small (11.2 months from start of treatment) and the survival rate at five years (50%) is not as high as that as stated in literature. The reasons for this can be appreciated from the initial steep portion of the survival curve and the large amount of clustering of censored data just about that point [Figure 6]. This steep initial portion of the curve represents the patients who dropped out of therapy at an early stage due to toxicity concerns or lack of finances to continue treatment. The steepness of the slope is also due to some toxicity related deaths in patients who could not afford supportive care during the periods of toxicity.

These facts present a different picture in our country. They impress upon us that our people are essentially poor (per capital income of India Rs. 23,222, almost equal to the

cost of six courses of CHOP). The poor educational levels often reflect the negative attitudes of our patients towards the right treatment. The lack of well equipped cancer centers that are easily accessible also add on to the misery of our hapless patients. There is a lacuna of medical insurance for the underprivileged hence our clientele is more often than not unable to afford state of the art treatment even when facilities are available.

According to the World Health Organization (WHO), 80% of health spending in India is in the private sector. The poorest is 2.6 times more likely to forgo medical treatment than the rich because the major pattern of spending in India is out-of-pocket spending.^[10] In this context, community health insurance (CHI) seems to be an equitable method which can help by:

- (i) improving access to healthcare among the poor; and
- (ii) protecting the poor from indebtedness and impoverishment resulting from medical expenditures.^[11]

A CHI maybe defined as “any not-for-profit insurance scheme that is aimed primarily at the informal sector and formed on the basis of a collective pooling of health risks, and in which the members participate in its management.”^[11,12] For wide acceptance a good CHI should have the following characters:

1. An effective and credible community based organization (or NGO). This is absolutely necessary as it is the foundation on which health insurance can be built.
2. An affordable premium-this is very important. It has been shown that people are ready to afford only Rs. 20-60 per annum in this regard.
3. A comprehensive benefit package is necessary to convince the community of the benefits of health insurance.^[11]

The first CHI in India was started in Kolkata as the Students’ Health Home and has been largely successful in catering to its target population. Several other schemes have emerged but lack in certain aspects especially in providing a comprehensive package and an affordable premium. Many schemes cover only a small “ceiling limit” and many do not cover the ambit of chronic diseases adequately.^[11] As India undergoes an epidemiologic transition from the epidemics of cholera to the pandemic of chronic diseases, these inclusions are imperative in our currently available small number of CHIs.

Despite the magnitude of the problem one cannot dismiss CHI as a drop in the ocean. It has a bright future in our country due to the fact that a good community based organization can help develop an effective community health insurance program. And India is teeming with such organizations-be it the trade movement, or the cooperative movement. Hospitals themselves can form an effective community base for people who need these kinds of insurances the most.

This will not only help patients in availing proper treatment but will also help physicians in improving the quality of care and using the latest innovations in medical science more

freely for the benefit of society. Thus for the physicians to successfully apply the recent advances in daily practices it is imperative to do away with the disparities in healthcare because as Dr. Martin Luther King Jr said “Of all the forms of inequity, injustice in healthcare is the most shocking and inhumane.”

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Source of Support: Nil, Conflict of Interest: None declared.

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