CASE REPORT

Ethics of a therapeutic trial: addressing limitations of an active intervention in optic nerve lymphoma

Rohan Bir Singh,^{1,2} Sahil Thakur,² Parul Ichhpujani,² Suresh Kumar²

¹Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts, USA

²Department of Ophthalmology, Government Medical College and Hospital, Chandigarh, Punjab, India

Correspondence to

Dr Rohan Bir Singh, dr.rohandhaliwal@gmail.com and Parul Ichhpujani, itdrparul@gmail.com

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SUMMARY

We report a unique case of optic nerve lymphoma after completion of chemotherapy for non-Hodgkin's lymphoma. The uncommon nature of presentation, our therapeutic dilemma and the further course of treatment are reported. In cases with extremely poor prognosis, unnecessary treatment puts additional strain both financially and psychologically on the patients and their family. Therapeutic focus should be on hospice care and family counselling. The decision to not treat is a crucial component of cancer management; however, the ethics of this decision are yet to be suitably addressed by the literature.

BACKGROUND

When to treat or not to treat is a question that plagues the mind of every physician taking care of terminally ill patients. This decision is especially vital because of its far-reaching economic, social and ethical consequences. It is estimated that in today's healthcare delivery system, up to 30% to 50% resources are wasted due to overtreatment.¹ Approximately 80% of all healthcare expenditures are attributed to physicians' decisions; thus, it is vital for every physician to rationally weigh the therapeutic as well as social, psychological and economic risk to benefit ratio in each case individually.² We report a case of refractory optic nerve lymphoma in a CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone)-treated non-Hodgkin's lymphoma (NHL (B-cell type IV (Ann Arbor staging)). Central nervous system (CNS) involvement occurs in approximately 10% of patients with NHL, and of these patients, about 5% may develop optic nerve infiltration.^{3,4} CNS involvement in NHL commonly occurs as secondary spread from systemic disease rather than as a primary CNS malignant neoplasm and carries a poor prognosis. The incidence of CNS involvement is increasing as newer treatment modalities result in longer survival and decreased mortality.⁵ Ophthalmologists hence are more likely to encounter patients with ophthalmic sequelae of NHL. This case presented to us with moral and ethical questions that we tried to answer to the best of our judgement.

CASE PRESENTATION

A 51-year-old Asian Indian woman diagnosed with NHL B-cell type IV presented to our outpatient department with decreased vision OS for the past

2 months. She had history of fractured right femoral head 1 year back, for which she underwent prosthetic hip replacement, and bone biopsy revealed NHL (CD20+). She subsequently completed eight cycles of CHOP regimen 2 months prior to ocular complaints.

INVESTIGATIONS

On examination, best corrected visual acuity in the right eye was 20/20 while left eye had visual acuity of finger counting 1 m, projection of rays accurate with relative afferent pupillary defect (RAPD). Examination of the adnexa, extraocular muscles and anterior and posterior segment was essentially normal in both eyes (figure 1). On MRI, focal areas of thickening and signal change were noted in the intracranial segment of the left optic nerve approximately 11 mmx6.5 mm. On T2 sequence, multiple sclerosed skull metastases were noted (figure 2). Visual fields revealed peripheral field loss in the right eye with enlargement of blind spot.

TREATMENT

Oncology consultation was sought; the patient was advised salvage chemotherapy keeping in mind the refractory metastasis. Rituximab, bendamustine and adalimumab were considered as reserve drugs, but the patient could not afford further therapy. The risk of toxicity with additional chemotherapy and poor prognosis associated with the spread to the optic nerve were explained to the patient and the family members. The decision to not treat was taken after full therapeutic disclosure and the patient was shifted to palliative care.

OUTCOME AND FOLLOW-UP

On follow-up after 2 weeks, the patient underwent repeat imaging, which showed bilateral optic nerve involvement with several newer metastases in the skull. Visual acuity reduced to 20/120 in the right eye and perception of light negative in the left eye. Visual field constriction was noted on subsequent visits in the right eye with compromised auditory function (moderate sensorineural hearing loss). The patient's general physical condition also deteriorated rapidly and she expired 4 weeks after optic nerve involvement.

DISCUSSION

Optic nerve involvement in a patient with systemic lymphoma often occurs from direct invasion by

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Figure 1 Clinical image montage showing normal extraocular muscle movements.

tumour cells, which tend to infiltrate cranial/spinal nerves and their meninges.⁵ Kim *et al* have reported a case of infiltrative optic neuropathy occurring as the sole manifestation of disease recurrence in a patient with systemic NHL otherwise thought to be in clinical remission.⁶ Besien *et al* studied the treatment of CNS recurrence in patients with NHL, and showed that intrathecal chemotherapy treatment did not result in meaningful responses while radiation therapy frequently resulted in transient, symptomatic relief.⁷ In our case, the patient had received CHOP regime which has been shown to be the most effective therapeutic regime for NHL.⁸ Rituximab, if given as the initial therapy, may have prevented the CNS recurrence as it has been shown to be better than conventional CHOP.⁹ It, however, could not be considered due to the financial status of the patient.

Over the last few decades, advances in monoclonal antibodies, drug-antibody conjugates, radioimmunotherapy and newer chemotherapy agents have led to improved prognosis of relapsed and refractory NHL. Unfortunately, still there is no therapeutic standard of care for salvage regimens, with prognosis after relapse remaining relatively poor.¹⁰ After the MRI evidence of optic nerve involvement and disease relapse, we offered the patient an option of a cerebrospinal fluid (CSF) tap and intrathecal chemotherapy, but it was refused by the patient. Radiotherapy was also offered as an alternative but the patient declined it too. The patient was also informed about the other chemotherapeutic agents available but the patient could not afford these costly drugs. We faced this therapeutic dilemma, whether to offer additional targeted chemotherapy, with additional financial strain

Figure 2 MRI showing focal areas of thickening and signal change in the intracanalicular segment of the left optic nerve approximately 11 mmx6.5 mm along with sclerosed skull secondaries. STIR: short tau inversion recovery sequence, CHOP: cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone.

and risk of adverse effects or to simply offer palliative care. Kim *et al*, in their review, report extremely poor prognosis of the disease when it reoccurs after chemotherapy. They suggest individually tapered management regimes as there are no clear-cut guidelines for salvage chemotherapy or optic nerve involvement.³ We hence realised that physician–patient communication regarding therapeutic expectations is very important. Weeks *et al* have shown that 69% of patients with lung cancer and 81% of those with colorectal cancer who had opted to receive chemotherapy had inaccurate expectations about the curative potential of chemotherapy. They also observed the relationship between inaccurate beliefs about the likelihood of cure and higher ratings of physician communication suggesting a link between physicians' communication behaviours and patients' understanding of treatment benefits. Their study shows how patients believe that physicians are better communicators when they convey a more optimistic view of chemotherapy.¹¹

The *et al* also demonstrate how patient's focus on regular follow-up visits and physician ambiguity about treatment and prognosis can lead to false optimism about recovery in the patient. The physician 'does and does not want to pronounce a death sentence, and the patient does and does not want to hear it'. The patients willingly accept the short-term treatment plans that involve tests and therapy while ignoring the long-term prognosis of the disease.¹²

In a review to evaluate judgements and decisions when cancer treatment is no longer curative in children under 19 years, Martinez *et al* reported that parents with inaccurate perceptions of the prognosis or unrealistic expectations for cure were more likely to choose aggressive therapies, including cancer-directed treatment, than those with more realistic expectations.¹³

Studies have shown that patients referred to hospice care often report that they were referred late. The perception of being referred too late, but not the actual length of stay, was associated with more unmet needs, lower satisfaction and more concerns.^{14–16} Hence, it may be better to take an early decision of not treating terminally ill patients, in order to give them a better quality of life in their final days, especially in countries where treatment is costly and not covered under insurance. Rabow *et al* have shown that seriously ill outpatients find palliative care more acceptable and helpful, reporting increased satisfaction and decreased healthcare utilisation.¹⁶

The question of end-of-life care in the low-income scenario still requires a lot of attention from all stakeholders like the

physicians, family members and most importantly the state.¹⁷ Any legislation on this issue however seems a distant dream. Another vital issue that stems from this case is the turmoil that a physician faces when deciding not to treat. Djulbegovic *et al* have elegantly described the models for therapeutic decisions, but completely miss out on the social, psychological and financial aspects of these decision models.¹⁸ We agree that our teaching system needs to focus more on the social engineering of these choices, which can affect not only the patient but also people around them. A careful review of all stakeholders rather than strict protocols is what should govern therapeutic choices in such patients.

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Learning points

- ▶ Patient's welfare should always be paramount while taking a therapeutic decision.
- ▶ Therapeutic trials on unproven regimes should only be done after full therapeutic disclosure.
- ▶ End-of-life care is a vital yet unexplored paradigm in ocular oncology.
- ▶ More discussion is needed on the ethics of subjecting patients to unnecessary procedures like an optic nerve biopsy in our case for someone who has already received cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone for lymphoma and has activity on positron emission tomography throughout the body.

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