VALUE IN HEALTH 16 (2013) 1123–1132

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Mifamurtide for High-Grade, Resectable, Nonmetastatic Osteosarcoma Following Surgical Resection: A Cost-Effectiveness Analysis

Sukhvinder Johal, PhD[1], *Stephen Ralston, MSc*[2], *Christopher Knight, MSc*[1,*]

[1]*RTI Health Solutions, Velocity House – Business and Conference Centre, Sheffield, UK;* [2]*Takeda Global Research & Development Centre (Europe) Ltd., London, UK*

ABSTRACT

Objectives: Mifamurtide is an immune macrophage stimulant that when added to standard chemotherapy has demonstrated survival benefit for newly diagnosed osteosarcoma. The objectives of this study were to investigate the cost-effectiveness of adding mifamurtide to standard three- or four-agent chemotherapy for high-grade, resectable, nonmetastatic osteosarcoma following surgical resection and the issues of obtaining robust cost-effectiveness estimates for ultra-orphan drugs, given the shortage of data. **Methods:** An economic evaluation was conducted from the perspective of the UK's National Health Service as part of the manufacturer's submission to the National Institute for Health and Care Excellence. The disease process was simplified to a transition through a series of health states, modeled by using a Markov approach. Data to inform the model were derived from patient-level data of Study INT-0133, published literature, and expert opinion. The final efficacy measure was life-years gained (LYG), and utilities were used to obtain quality-adjusted life-years (QALYs). **Results:** For a 60-year time frame and a discount rate of 3.5% for outcomes, patients receiving mifamurtide benefited from an average additional 1.57 years of life and 1.34 QALYs, compared with patients receiving chemotherapy alone, giving an incremental cost-effectiveness ratio (ICER) of £58,737 per LYG and £68,734 per QALY. Because treatment effects were both substantial in restoring health and sustained over a very long period, the National Institute for Health and Care Excellence changed its guidance to allow a discount of 1.5% for outcomes to be applied in these special circumstances. By using this discount factor, it was found that patients receiving mifamurtide had an average additional 2.58 years of life and 2.20 QALYs compared with patients receiving chemotherapy alone, resulting in an ICER of £35,765 per LYG and £41,933 per QALY. **Conclusion:** Mifamurtide's ICER is cost-effective compared with that of other orphan and ultra-orphan drugs, for which prices and corresponding cost-effectiveness estimates are high.

Keywords: cost-effectiveness analysis, discount rate, NICE appraisal, osteosarcoma, ultra-orphan.

Background

Osteosarcoma is the most common type of primary bone tumor and usually occurs during childhood and adolescence [1]. Its incidence varies with age, with an annual incidence rate of 7.3 cases per million for adolescents (aged 15–19 years) for the period 1988 to 1997 in the United Kingdom [2]. The disease has an estimated annual incidence rate of 2.6 cases per million for children (aged 0–14 years) for the period 1988 to 1999 [3]. These data on osteosarcoma indicate that approximately 73 children, adolescents, and young adults present with osteosarcoma per year in the United Kingdom, with 58 (80%) of these individuals having high-grade, nonmetastatic disease [4–6]. Osteosarcoma can be considered an "ultra-orphan" disease, a term used to describe very rare diseases, as distinct from more common orphan diseases. The National Institute for Health and Care Excellence (NICE) defines a disease as ultra-orphan if it has a UK prevalence of less than 1 in 50,000 and if there are fewer than 1,000 cases per year [7].

The management of patients with osteosarcoma is complex and aims to completely remove all clinically detectable tumors surgically and to control microscopic metastatic disease via systemic polychemotherapy [8]. The aim is to increase the survival rate and prevent recurrence of the disease. The treatment pathway is generally composed of neoadjuvant chemotherapy, followed by optimal surgery to remove the entire primary tumor and to render the patient disease free, with a subsequent course of adjuvant chemotherapy being administered to target micrometastases. Young people who undergo successful surgery for osteosarcoma are able to live full lives, and they have a quality of life similar to that of their peers although prosthetic limbs and endoprostheses will need to be replaced as they grow [9].

There are currently no standard recommended combinations of chemotherapy drugs, and the optimal treatment duration is yet to be defined [10]. There currently, however, are four chemotherapeutic agents with well-established efficacy in treating osteosarcoma: doxorubicin, cisplatin, high-dose methotrexate with leucovorin rescue, and ifosfamide. Currently, 60% to 70% of the patients having high-grade, nonmetastatic osteosarcoma achieve long-term, disease-free survival following these three- or four-agent neoadjuvant and adjuvant chemotherapy regimens

* *Address correspondence to:* Christopher Knight, BresMed Health Solutions, North Church House, 84 Queen Street, Sheffield S1 2DW, UK. E-mail: cjknight1001@gmail.com.

1098-3015/$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2013.08.2294

[11,12]. Since the introduction of standard chemotherapy, no new drugs with proven efficacy have been added to the standard therapeutic armamentarium [8]. Various studies have suggested that the combination of multiagent chemotherapy with biologic-response modifiers and immune activators may achieve additional treatment benefits [10].

Mifamurtide is an immune macrophage stimulant. It has a marketing authorization for use in children, adolescents, and young adults for the treatment of high-grade, resectable, non-metastatic osteosarcoma after macroscopically complete surgical resection, and has been safely administered together with standard adjuvant chemotherapy in patients aged between 2 and 30 years.

The largest ever completed, randomized phase III trial of treatments for patients aged 30 years or younger with newly diagnosed osteosarcoma initiated in 1993 was reported by Meyers et al. [13,14]. Among the 793 patients who enrolled in the trial, 115 patients had either clinically detectable metastases or an unresectable primary tumor at study entry. Of the 678 remaining patients, 16 were considered ineligible. Among the remaining 662 patients without metastases and resectable tumors, 361 patients were male and 301 were female. The trial results have demonstrated a survival benefit when mifamurtide is added to a chemotherapy regimen, with the 6-year survival rates increasing from 71% to 75% for patients on three-agent chemotherapy and from 70% to 81% for patients on four-agent chemotherapy. For all patients, the overall 6-year survival rate when mifamurtide is added to a chemotherapy regimen increased from 70% to 78% ($P = 0.03$) [14]. The median age of patients in this trial was 13 years. The median follow-up duration for the trial, from commencement of the maintenance phase, was 7.7 years while the maximum follow-up duration was 12.25 years [14]. The clinical trial, despite its weaknesses in standards and procedures, provided a good source of data for an ultra-orphan disease, because of study sample size and long-term follow-up.

The cost-effectiveness of mifamurtide treatment in this patient group has not previously been published, although the manufacturer of mifamurtide recently made a submission to NICE that included a cost- effectiveness analysis for mifamurtide as an add-on to multiagent chemotherapy compared with multiagent chemotherapy alone [15]. The decision-analytic model and subsequent cost-effectiveness analysis presented here formed part of the manufacturer's submission to NICE.

Like other ultra-orphan diseases, data shortages, due to the limited number of clinical trials in osteosarcoma and difficulties with recruiting the number of patients needed to adequately power such a trial, mean that the level of uncertainty associated with clinical effectiveness for mifamurtide is greater than for drugs for prevalent diseases. Hence, this article lays out not only how the cost-effectiveness analysis was assessed but also what the difficulties were in trying to develop cost-effectiveness models in this disease area.

Methods

Model Structure

For the purposes of the economic analysis, the disease process was formulated as a transition through a series of health states, modeled by using a Markov approach (Fig. 1). The comparator treatment used for assessment of the decision problem was the three- or four-agent chemotherapy regimen alone, which represents the current UK treatment approach.

Patients entered the model in the disease-free state after surgical resection and remain in this state unless they have a recurrence or die. Following a recurrence, patients could move either to a postrecurrence disease-free state or to a postrecurrence disease-progression state. The first cycle in the disease-free state represented the chemotherapy maintenance phase, in which all patients received adjuvant chemotherapy with or without mifamurtide. This cycle had a length of 9 months. Thereafter, cycles had a length of 6 months. Patients moved among states during each cycle. Once patients entered the disease-progression state, the model made the assumption that they remained there until death. Patients in the disease-free health state at the end of the trial period (12.25 years) were assumed to have a mortality rate equivalent to that of the general population. The model used estimates of effectiveness, costs, and health-state values in these health states to model progression of disease and cost-effectiveness over time. Costs and outcomes were discounted at 3.5% per annum, in line with NICE guidance [16].

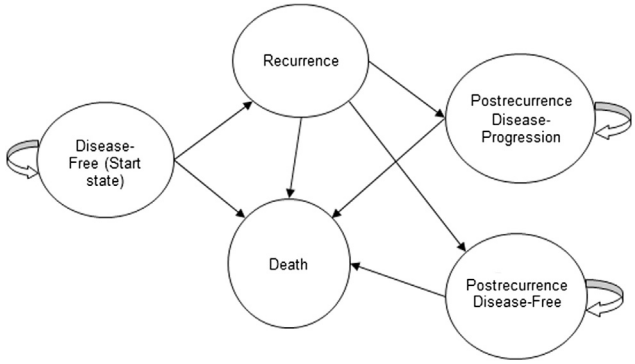

Fig. 1 – Markov model structure.

As mifamurtide is indicated for children, adolescents, and young adults, with the potential for a long life expectancy, a time horizon of 60 years was considered as the base case. Other time horizons were considered in the sensitivity analysis.

The number of patients exiting the disease-free state at the end of each 6-month cycle was governed by time-dependent transition probabilities of recurrence and death. Actual patient numbers, from patient-level data collected in the trial, were used to compute transition probabilities for each 6-month period, with patients lost to follow-up attributed to a health state based on the transition probabilities derived from those patients not lost to follow-up.

Patients who experienced a recurrence in the trial were not routinely followed up, and those who were lost to follow-up were reported as withdrawals. The clinical literature reported that the risk of survival postrecurrence was dependent on the site of recurrence, and that site was a determinant for achievement of disease- free status and survival postrecurrence. Of those patients in the trial whose disease did recur, approximately 85% of the patients in both treatment groups experienced disease recurrence at a pulmonary location or other (pleural, regional, radiation field, mediastinal, lymph node) sites. In the trial, approximately 50% of the patients had pulmonary metastases only.

Because the literature indicated that the risk of death postrecurrence was different for patients achieving disease-free or non–disease-free status postrecurrence, it was considered important to factor literature findings into the model and include an analysis of events postrecurrence.

Data from Ferrari et al. [17] were used to calculate remission rates from surgery or a combination of surgery and second-line chemotherapy. The Ferrari et al. study reported findings from 162 patients with recurrent osteosarcoma (75% of whom had lung metastases) who received first-line treatment, including