



Year 2006 Update of the National List of Health Services – An Endless Process

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In March 2006 the Public National Advisory Committee for the addition of new medical technologies to the National List of Health Services in Israel concluded its first round of discussions for the year 2006 and recommended the inclusion of 28 drugs and other medical technologies to the NLHS, at a cost of NIS 467 million (US\$ 104 million) per year. However, at that time, the government had decided to allocate only NIS 310 million (US\$ 69 million) for that purpose, leaving many important drugs and other technologies out of reach for most of the patients who needed them. This situation, aggravated by a shortage of budgetary allocations for updating the NLHS in previous years, led to an outburst of frustration among patients and their families because extremely expensive drugs for treating their illnesses have not been reimbursed.

The most prominent protest came from colon cancer patients, who initiated a hunger strike in order to promote public funding of two “biologic” target-specific drugs for the treatment of metastatic colon cancer: bevacizumab (Avastin®, Hoffmann-La Roche) and cetuximab (Erbix®, Merck KGaA). This protest led to the allocation of an additional NIS 390 million (US\$ 87 million) at the expense of the budget to be allocated for the 2007 NLHS update, resulting in a total budgetary allocation of NIS 700 million (US\$ 156 million) for the year 2006. This combined 2 year budget has enabled supplementing the NLHS with all the drugs and technologies recommended by the Committee, including some life-prolonging drugs for metastatic cancer patients.

The article by Tamir et al. in this issue of *IMAJ* [1] illustrates the rigorous and complicated process of updating the national list of publicly funded technologies in 2006. The basic task of the Public Advisory Committee is to prioritize the submitted technologies for listing, based on their value for improving health outcomes, their cost and other guiding criteria. The process of prioritizing oncology drugs is of special interest, since their cost

is usually very high and there is considerable (and sometimes even aggressive) public and political pressure to include all these pharmaceuticals in the NLHS.

Bevacizumab was first added to the NLHS in 2005 for the treatment of two subgroups of metastatic colorectal cancer patients: a) metastatic rectal cancer patients, for whom the treatment adds 9 months to the overall survival; and b) patients with metastases located in one central site, who are candidates for curative surgery. The addition of bevacizumab to the pre-surgical treatment might shrink the metastases and increase the chances of total removal of the cancer tissue, thus curing the patient. This year bevacizumab is to be included in the NLHS in its wide indication as a first-line treatment for *all* metastatic colon cancer patients, and for local recurrent rectal cancer.

Cetuximab was also a candidate for inclusion in the NLHS for two indications: a) as second- and third-line treatment for metastatic colon cancer patients, and b) as upfront treatment combined with radiation for patients with locally advanced squamous cell cancer of the head and neck. According to the Committee’s recommendation only the second indication is to be added to the NLHS.

A phase III study by Hurwitz and collaborators [2] published in the *New England Journal of Medicine* indicates a 5 month prolongation of the overall survival by adding bevacizumab to IFL (irinotecan, 5-fluorouracil, leucovorin) first-line chemotherapy. As for cetuximab, a phase II study by Cunningham et al. published in the same journal [3] could not indicate any prolongation of the overall survival by adding cetuximab to the second- or third-line protocols, since there was no control arm. In fact, there are no published phase III placebo-controlled studies that examine the efficacy of cetuximab as a second- or third-line treatment for metastatic colon cancer.

The cost of treating one colon cancer patient with bevacizumab is NIS 160,000 (US\$ 35,600), as compared to NIS 108,000 (US\$ 24,000) with cetuximab. In addition to the 350 patients

NLHS = National List of Health Services

eligible for bevacizumab treatment for the indications included in 2005 in the NLHS, there are 550 additional patients anticipating treatment with bevacizumab in its wider indication. Thus, the total annual cost for the inclusion of bevacizumab in the NLHS for all metastatic colorectal cancer patients is NIS 125 million (US\$ 28 million). The annual cost of cetuximab for second- and third-line treatments for metastatic colon cancer patients is about NIS 108 million (US\$ 24 million) for 1000 patients, while limiting its funding for only third-line treatment would restrict its use to 350 patients at a national cost of NIS 38 million (US\$ 8.5 million) per year. Therefore, publicly funding bevacizumab and cetuximab for all metastatic colorectal cancer patients would amount to a cost of NIS 163 to 233 million (US\$ 36–52 million) per year at the national level. Based on their cost and efficacy figures, the incremental cost of adding one life-year for a metastatic colon cancer patient treated with bevacizumab is NIS 408,582 (US\$ 90,796), while the cost of adding one life-year for a patient treated with cetuximab is infinite, since the current evidence does not indicate any effect of cetuximab on the overall survival.

During its first round of discussions, the Committee found that the cost-effectiveness ratio of bevacizumab and cetuximab for the treatment of colon cancer patients was inferior compared to other technologies for the treatment of cancer. This decision was consistent with the recommendations of the Israel National Council of Oncology, which classified these two drugs as inferior to other oncology drugs under discussion, due to their limited efficacy on one hand and their very high costs on the other. During the second round of discussions of the Committee, according to the revised recommendations of the Israel National Council of Oncology, a decision was made to include bevacizumab in the NLHS for first-line treatment of all metastatic colorectal cancer patients, but *not* to include cetuximab for second- or third-line treatment of the disease, due to lack of evidence of its effectiveness as well as its high cost. However, the other indication submitted for cetuximab – treating patients with locally advanced head and neck cancer – was eventually recommended for inclusion in the list.

One oncology drug that was classified by the Israel National Council of Oncology as top priority among all the oncology drugs under discussion is trastuzumab (Herceptin®, Hoffmann-La Roche) for the adjuvant (post-surgical) treatment of HER2-positive early-stage breast cancer. Studies [4,5] have shown a dramatic 50% reduction in cancer recurrence among patients treated with adjuvant trastuzumab for one year, and an absolute 18% reduction of recurrence at 4 years of follow-up. The per-patient cost of adjuvant trastuzumab is about NIS 200,000 (US\$ 44,444). It has been estimated that 585 patients will receive the treatment each year, at a national cost of NIS 115 million (US\$ 25.5 million). According to the results of a National Cancer Institute study [5], treatment of 585 patients per year with adjuvant trastuzumab is expected to prevent recurrence in 18% of them at 4 years of follow-up, which means the prevention of cancer recurrence in 105 women every year. Taking into consideration that recurrent HER2-positive breast cancer is in most cases a metastatic one,

thus non-curative, it is most probable that for those 105 women adjuvant trastuzumab is a life-saving therapy. Based on its cost and efficacy, the cost of preventing recurrence of cancer in one patient treated with trastuzumab is expected to be NIS 1.1 million (US\$ 244,444). Assuming that prevention of recurrence of metastatic breast cancer leads to a minimum 10 year prolongation of overall survival, the cost for one additional life-year gained would be at maximum NIS 110,000 (\$24,444), which is almost fourfold lower – and therefore much more cost-effective – than bevacizumab.

At the time of the National Committee's discussions trastuzumab had not yet been approved for the adjuvant indication in Israel or in any other western country. Nevertheless, the Committee decided not to wait for the regulatory approval of the adjuvant indication and recommended its immediate inclusion in the NLHS. In spite of this, the Ministry of Health has decided not to do so until a regulatory approval is granted in Israel after an approval has been issued in another western country. In June 2006, the European Union's regulatory agency (EMA) approved the use of trastuzumab for its adjuvant indication. In light of this approval, the Israel Ministry of Health decided to speed up the local regulatory approval process in order to include it in the NLHS as soon as possible. On 1 July 2006 the adjuvant indication of trastuzumab was approved and included in the NLHS.

It is interesting to analyze listing timelines of the above-mentioned technologies in an international context. For instance, in the final appraisal determination of 21 August 2006, the National Institute for Health and Clinical Excellence of England and Wales decided not to recommend publicly funding bevacizumab and cetuximab for the treatment of metastatic colorectal cancer [6]. In Australia, cetuximab was also rejected at the July 2006 Pharmaceutical Benefits Advisory Committee meeting [7]. Decisions swept in a different direction for adjuvant trastuzumab. On 22 August 2006, the Australian Ministry for Health and Aging announced that the Commonwealth Government will list trastuzumab on the Pharmaceutical Benefits Scheme from the 1 October 2006 for the treatment of patients with HER2-positive early-stage breast cancer following surgery [8]. Similarly, on 23 August 2006, NICE issued final guidance to the National Health Services, recommending trastuzumab for women with early-stage HER2-positive breast cancer (but stating limitations related to concerns about the women's cardiac function). This occurred only 3 months after the drug was licensed by the British regulatory authorities for use in the adjuvant indication [9], in contrast to the accelerated process in Israel.

Another life-saving technology discussed this year is the ultra-orphan drug alglucosidase (Myozyme®, Genzyme Corporation) for the treatment of Pompe disease – a fatal genetic deficiency of acid alfa-glucosidase enzyme. Alglucosidase is a recombinant enzyme replacement capable of preventing disease deterioration and keeping the patient alive. Although the average annual cost per patient is above NIS 1 million (US\$ 222,222) per year and the incremental cost-utility ratio appears to be well above the

NICE = National Institute for Health and Clinical Excellence

maximum accepted threshold of US\$ 100,000 per QALY (quality adjusted life-year), the Committee decided to publicly fund this treatment and include it in the NLHS. The amount of NIS 13 million (US\$ 2.9 million) was allocated for the treatment of seven current Pompe patients. This decision is consistent with the Committee's basic perception from its outset, derived from the Jewish belief in the sacredness of life, that any true life-saving technology (a technology that results in a substantial prolongation of life) should be publicly funded, particularly if its cost per patient is very high and therefore non-affordable by most patients from their own private resources.

Although a major budgetary stride forward, the combined 2006 and 2007 budget of NIS 700 million (US\$ 156 million) is still a one-time solution that will not prevent similar harsh situations in the future – namely, patients with severe illnesses who are not able to fund the medical treatment they need. With reference to the required annual allocation of 2% of the total NLHS budget, the actual updates of the NLHS during the years 1998 to 2006 have resulted in a cumulative deficiency of approximately NIS 1.6 billion. While the Israeli publicly funded list of health services, to which all residents are entitled, is still considered to be one of the most generous in the western world, the experience of recent years indicates that many important and essential technologies were not included in the NLHS.

In the future, new emerging technologies will continue to pave the way to better health outcomes. This will require scrupulous budgeting considerations within a rigorous methodical mechanism. Although we have established a unique systematic health technology assessment process in Israel [10], there is a need for a better model for resource allocation that will ensure an ongoing process to maintain a high level of healthcare.

I believe there should be a permanent solution to the severe social problem described here, whereby a constant annual monetary addition, mandated by law, will be enacted at the level of 2% of the total NLHS budget. Furthermore, there is a consensus among opinion leaders in the field, based on the literature, that such an amendment to the National Health Insurance Law is necessary for maintaining the high level of public healthcare

services in Israel. I believe that it is not only morally important, but also medically imperative to maintain an ongoing updated “basket” of health services in Israel to continually improve health outcomes.

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