Cancer vaccines and immunotherapeutics

Challenges for pricing, reimbursement and market access

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Public payment is key to market access for new therapeutics including cancer vaccines and cancer immunotherapeutics. However, the methodology for economic evaluation aimed at informing decisions about pricing and reimbursement is different for cancer vaccines, such as HPV for preventing the occurrence or incidence of cancer, and immunotherapeutics for treatment of patients with manifest cancer. Vaccination against HPV is a traditional public health intervention, where the role of economic evaluation is to inform decisions about optimal vaccination strategies. The decision is about funding for a vaccination program, aimed at vaccinating a defined population at risk, either at a national or regional level. The methodology of economic evaluation is based on statistical modeling of number of cases prevented over a long time period, and the costs and health outcome related to this, for different vaccination strategies.

For immunotherapeutics, the role of economic evaluation is to assist decisions about reimbursement and guidelines for treatment of patients with established disease, very often at advanced stages with short life expectancy. The focus is on alternative treatment options, and the costs and outcomes associated with these. Alternatives may be best supportive care, immunotherapeutics or other treatments like surgery, radiotherapy and other anti-cancer drugs. From an economic perspective the type of therapy does not matter, only costs and outcome associated with the relevant alternatives. The main controversy about

reimbursement of immunotherapeutics, as with other new cancer drugs, has been the cost of treatment, mainly determined by the price of the therapy, in relation to the expected benefits in terms of survival and quality of life. This paper reviews the evidence on cost-effectiveness, the reimbursement decisions made, and the impact on market access for new immunotherapeutics. Sipuleucel-T (Provenge®) and abiraterone (Zytiga®) for treatment of prostate cancer and ipilimumab (Yervoy®) as well as vemurafenib (Zelboraf®) for treatment of metastatic melanoma are used as examples of the economic issues involved in analysis and decision-making.

Introduction

The aim of this paper is to review the economic aspects of pricing, reimbursement and market access for cancer vaccines and immunotherapeutics. We will comment on the general trend assessing the cost-effectiveness of new cancer treatments to inform decisions about, pricing, reimbursement and market access as well as the specific issues related to cancer vaccines and immunotherapeutics. The key question is if cancer vaccines and immunotherapeutics differ from other cancer therapies from an economic perspective?

Economic Evaluation of HPV Vaccination Programs

Human papillomavirus (HPV) infections have been associated with a number of cervical and non-cervical diseases,

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including cervical cancer. HPV vaccines have been licensed for use in females for some time, and many countries have adopted a vaccination program for adolescent females based on results of cost-effectiveness analyses.¹ Economic evaluations have also studied the cost-effectiveness of extending the vaccination to boys and young (homosexual) males as well as multi-cohort strategies for women.² Focus has been on the reduction in risk for cervical cancer, but also on head-neck cancer as well as on non-cancer outcomes like sexual transmitted genital warts. All these aspects have been included in comparisons of different types of vaccines and vaccination strategies.

Economic evaluation of HPV vaccination programs follows closely the methodology for previous studies of vaccination against other infectious diseases, going back to early economic studies of vaccination against polio. The studies are undertaken to inform a public health decision about implementation of a vaccination program, and the social costs and benefits from such a program are calculated. While the general methodology is well established, studies differ in terms of which costs that are included and how outcome is measured. In studies of HPV vaccination the most common outcome measure is quality adjusted life years (QALY) gained, and the costs both within and outside the health care system are included. Cost-effectiveness is determined by the price of the vaccine and the number of cases prevented. The latter is estimated in a statistical model based on data from clinical studies of efficacy and epidemiological studies of risk of infection and transmission to disease.

Modeling cost-effectiveness of vaccination programs involve estimating of long term effects and results are surrounded by uncertainty, particularly related to modeling of herd immunity and externalities, as well as rare potential side effects. However, there is still a general belief that such modeling is contributing to better-informed decisions, and most countries require such studies as a basis for decision making.^{3,4} Still, public decisions about vaccination programs are to large extent strategic decisions, where the final decision includes political factors as well.

Sipuleucel-T (Provenge®), and Economic Evaluation of Therapeutic Cancer Vaccines

Therapeutic vaccines that stimulate the immune system to recognize and attack certain cancer-associated proteins are new treatment options in cancer. Renal cancer and melanoma have been the main focus for this development, but other tumour types like prostate cancer have been explored. Additional strategies that combine vaccines and standard therapeutics, including radiation, chemotherapy, targeted therapies, and hormonal therapy, must be assessed in terms of outcome and costs. One such vaccine, sipuleucel-T (Provenge®), was FDA-approved for the treatment of metastatic prostate cancer in 2010, and we will use this to illustrate the issues raised in the discussion around assessment of value for pricing, reimbursement and market access. For a review of on-going trials of cancer vaccines in prostate cancer, see Joniau et al.⁵

Sipuleucel-T is an autologous cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. Sipuleucel-T is made using cells from a patient's own immune system, so it cannot be warehoused like many other drugs and requires specialized manufacturing facilities. Sipuleucel-T is designed to stimulate a patient's immune system to target prostate cancer cells. The process of making Sipuleucel-T involves the exposure of a patient's immune cells to a protein that functions as a prostate cancer-associated antigen. This process activates the patient's immune cells against prostate cancer.⁶

The clinical efficacy of sipuleucel-T is demonstrated in three phase 3 controlled and double-blinded trials (D9901, D9902A, and D9902B) that enrolled a total of 737 patients. The largest of these three trials, called Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT), has demonstrated safety and effectiveness of sipuleucel-T as measured by prolonged survival of 512 asymptomatic patients with metastatic castration-resistant PCa (mCRPC). The study showed a 4.1-mo median survival benefit

in the sipuleucel-T vaccine-treated group compared with the control group [25.8 vs. 21.7 mo; hazard ratio (HR): 0.78; 95% confidence interval (CI), 0.62-0.98; $p=0.032$] and extended 3-yr survival (31.7% vs 23.0%).⁵

So far no economic evaluations of treatment strategies involving sipuleucel-T have been published, but there has been a discussion about cost-effectiveness in relation to reimbursement in the US. The price of \$93,000 per treatment is one aspect of the reimbursement discussion, but also other aspects related to doctor's payment for administering the drug have contributed to a slower market uptake than expected. Major insurers as well as Medicare (after a yearlong review) reimburse the treatment, and the company offers assistance for patients to receive reimbursement.⁷

With an estimated cost of \$93,000 and an expected survival gain of 4.1 mo, the cost per life year gained is \$280,000. While this is in the ballpark for what US physicians accept as a benchmark for cost-effectiveness, it is significantly higher than UK (£50,000/\$80,000) and Sweden (1 million SEK/ \$150,000) would consider as an acceptable cost-effectiveness ratio.⁸ European estimates also take into account other costs associated with the treatment, as well as a quality of life adjustment. Even if those extra costs are considered marginal, no estimates have been provided so far, and even if the quality of life of the extra months can be expected to be good with immunotherapy, it is reasonable to expect that the reimbursement hurdle will be even greater in Europe.

One indication of what is to expect can be seen from the recent reimbursement decisions for abiraterone (Zytiga®), which has a similar indication as sipuleucel-T. The Swedish reimbursement agency, TLV, said no to the reimbursement application, since the costs per QALY was over the \$1 million informal benchmark value.⁹ NICE in the UK and the Scottish Medicines Consortium (SMC) also rejected reimbursement.¹⁰ However, after discussions with the manufacturer, NICE accepted reimbursement in the major indication after being offered a discount in price, which got the cost per QALY below £50,000.¹¹ We can expect that there will be further negotiations of market access

schemes in other jurisdictions in Europe, following this decision.

The price of abiratorone is £2,930 (\$4,400) per month, which makes the total cost dependent on the length of the treatment. The US whole-sale price indicate an annual treatment cost of \$48,000, which is comparable to that of cabazitaxel (Jevtana®), another new treatment for metastatic PCa. New treatments like MDV3100 and Alpharidin are on their way to the market in the same indication, which makes for interesting and important studies of costs and outcome to inform reimbursement and treatment decisions. Which patients should have what drug, and what are the costs and outcome of combining the treatments?

Ipilimumab for Treatment of Metastatic Melanoma

Ipilimumab (also known as MDX-010 or MDX-101), is a drug used for the treatment of metastatic melanoma. Cancer cells produce antigens, which the immune system can use to identify and destroy them. These antigens are recognized by dendritic cells, which present the antigens to CTLs (Cytotoxic T lymphocytes that can recognize and destroy cancer cells) in the lymph nodes. The CTLs can then recognize the cancer cells by those antigens and destroy them. However, dendritic cells also present the antigens to CTLs along with an inhibitory signal, which binds to a receptor, CTLA-4 (cytotoxic T lymphocyte-associated antigen 4), on the CTL and turns off the cytotoxic reaction. This allows the cancer cells to survive. Ipilimumab blocks the CTLA-4 inhibitory signal, and allows the CTLs to destroy the cancer cells. Ipilimumab is a fully human antibody that binds to CTLA-4. It was approved by FDA and EMA in 2011.¹²

There have been two major issues around ipilimumab, at least in Europe. One has been the price of the drug (\$120,000) and the other has been a discussion around the magnitude of effect generated by ipilimumab treatment. The median survival benefit is estimated (in second line at a dose of 3 mg/kg) to be just short of 4 mo. Based on this, the cost of

one life year gained would come at a cost of \$350,000.

If one, on the other hand, instead base the decision on the mean survival gain, the cost per life year gained will change substantially.¹³ In a recent assessment by the Swedish TLV, the survival benefit was estimated to be around 13 months, thus generating a cost per life year gained of around \$100,000, and a cost per QALY of \$140,000.¹⁴ This means that ipilimumab at present is slightly above (+5–10%) the Swedish threshold for reimbursement. The problem is that we do not know with certainty the mean survival for some time.

The solution for market access in Sweden, as in other European countries, is presently linked to discussions around discounts and agreements about selection and number of patients treated and collection of data to verify outcome and costs. In addition to melanoma, ipilimumab is undergoing clinical trials for the treatment of non-small cell lung carcinoma (NSCLC), small cell lung cancer (SCLC) and metastatic hormone-refractory prostate cancer.

During 2011–12 both FDA in the US and EMA in EU approved another drug, vemurafenib (Zelboraf®), for the treatment of metastatic melanoma. This is not an immunotherapeutic drug, but a small molecule that acts like a B-Raf enzyme inhibitor in patients with V600 E B-Raf mutation. The drug has shown very high anti-tumor activity (> 50% response rate), but the response duration is relatively short in some patients leading to a median survival benefit of 3.6 months.¹⁵ This drug comes at a monthly cost of \$9,400 and a median treatment time of 6 months leading to a cost per LYG of just over \$200,000. The costs for identifying the 50% of patients that can benefit are paid by the manufacturer (\$120–150/test), but the health care system has the costs for organizing collection of samples. The fact that vemurafenib has an accompanying diagnostic that can identify which patients that can benefit from treatment is seen as an advantage, but it does not seem to have a major impact on the reimbursement decision. The main criteria is still the survival benefit in relation to costs, as is shown

by the on-going negotiations in NICE evaluation of vemafurinib.¹⁶

Conclusions

Cancer vaccines are a new and important treatment option to reduce the burden of cancer. But it is important from a pricing, reimbursement and market access perspective to make a distinction between preventive vaccines that help immune system to fight off specific microorganisms, and therapeutic vaccines that stimulate the immune system to recognize and attack certain cancer-associated proteins. Preventive vaccines, like HPV should be compared with other public vaccination programs, as an option to invest in reduction of the incidence of cancer. There is a long tradition in undertaking economic evaluations of vaccination programs, and the decision-making process and payment for such programs are usually different from that for cancer drugs. Economic aspects are important, but since it is a technology aimed at preventing disease in healthy individuals, the safety aspects as well as public perceptions about such programs are important for the decisions. Economic evaluations have contributed to general acceptance of a strategy to vaccinate adolescent girls against HPV, but policy responses differ between countries.

Therapeutic vaccines are new treatment modalities, which compete with and complement other treatment options. While immunotherapy may offer advantages in terms of fewer side effects and improved quality of life, it is the total impact on survival, quality of life and quality of care that will determine the optimal treatment strategy. We will see more requests for follow up studies in clinical practice as a new treatment for cancer is first developed for the most severe stages of the disease, and the evidence on impact on survival and quality of life is often limited when it comes to the market. Such follow-up studies are needed, not only to answer questions about outcome, but increasingly also about costs and cost-effectiveness; market access is not only about price discounts, but also the selection of patients for treatment. With so many new cancer treatments entering the market, costs cannot be ignored,

and there is a need for an improved collaboration between manufacturers and payers to make sure that no drugs will not be left on the side lines due to lack of ability of the different stakeholders to reach agreements. The stakes are too high for that. Information and costs and cost-effectiveness to inform decisions about pricing, reimbursement and market access must be an integrated part of the development of evidence based cancer care.

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