Editorial

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Practical and clinical benefits of radioimmunotherapy lead to advantages in cost-effectiveness in the treatment of patients with non-Hodgkin's lymphoma

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Introduction

The recent development of radioimmunotherapy (RIT) is a significant step forward in the treatment of patients with low-grade and follicular non-Hodgkin's lymphoma, a malignancy that is well known to be inherently radiosensitive. Highly convincing efficacy [1–3] and safety [4] data are now available to support the benefits of RIT in follicular lymphoma. In addition, RIT offers significant quality of life benefits to patients [1,2] and convenience when compared with older chemotherapy combinations.

Despite the advantages of RIT, its routine use in follicular non-Hodgkin's lymphoma currently poses a number of challenges. These include the need for hospitalization in some regions, practical safety concerns, the need for interdisciplinary cooperation and the need for adequate budgets for RIT therapy at a time when there are increasing numbers of other high-cost oncology products reaching the market. Each challenge to the widespread availability and use of RIT must be dealt with to ensure that all suitable patients have access to this new and innovative therapy.

Radioimmunotherapy

Therapy with radioimmunoconjugates has been extensively tested clinically using murine anti-CD20 monoclonal antibodies (MAbs) conjugated to either ^{131}I (^{131}I-tositumomab [Bexxar; Corixa Corporation, Seattle, Washington, and GlaxoSmithKline, Philadelphia]) or ^{90}Y (^{90}Y-ibritumomab tiuxetan [Zevalin; BiogenIdec, San Diego, USA and Schering AG, Berlin, Germany]) [5]. Studies employing one or the other radioimmunoconjugate have demonstrated significant therapeutic benefit for patients with follicular non-Hodgkin's lymphoma and both therapies are considered to be similarly efficacious in this indication. The relative merits of both radioimmunoconjugates with respect to practical issues, including radiation exposure risk and other parameters that could affect a patient's quality of life as well as overall costs to the health care system are important differentiators of treatment choice.

Hospitalization and time commitments for medical staff and patients

The radionuclide ^{90}Y does not produce penetrating gamma radiation, and patient isolation and lead shielding are therefore unnecessary. Accordingly, hospital-based outpatient therapy is feasible with ^{90}Y and no isolation from family or friends is required. In contrast, the ^{131}I-labelled antibody requires inpatient hospitalization due to the inherent risk of exposure from gamma emissions, and patients and families need to follow detailed instructions to prevent undue exposure. A further advantage of the ^{90}Y product and an issue that is of relevance to both patients and medical staff is the need for dosimetry to calculate effective therapeutic doses with the ^{131}I-labelled antibody, which is not required for ^{90}Y. Finally, from a cost and resource point of view, the provision of hospital beds under radiation protection for inpatient radioimmunotherapy using radionuclides with a gamma component such as ^{131}I would be a major challenge if the product was to become more widely used.

Practical safety

Eschner *et al.* undertook an interesting radioecological calculation on radioactive excretions of patients assuming treatment with ^{90}Y-labelled ibritumomab tiuxetan on an outpatient basis [6], indicating that, apart from ^{90}Y-ibritumomab tiuxetan, there is room for many more radioimmunotherapies using ^{90}Y as the radionuclide without the necessity for implementing any inpatient infrastructure. Indeed, according to the very recent recommendation of the German Radiation Protection Commission, in 2005, an outpatient treatment with ^{90}Y-ibritumomab tiuxetan in Germany in the approved dosage is permissible in institutions which fulfil the necessary requirements for handling open radioactive substances [7].

The only reasons for indicating hospitalization of patients treated with ^{90}Y-labelled ibritumomab tiuxetan would be if there was a need to monitor co-morbidities, or if there were complications arising from the treatment or

if there was a special need for radiation protection such as small children or pregnancy in the patient member environment. Only for the latter situation would hospitalization to a nuclear medicine ward be indicated.

The debate on whether the use of radioimmunotherapy is associated with an increased risk of developing treatment-related myelodysplastic syndrome (tMDS) and acute myelogenous leukaemia (AML) has sometimes led to concerns by haemato-oncologists in recommending new radioimmunotherapies to patients. However, based on new long-term data available on the development of tMDS/AML after radioimmunotherapy [8], which show no increased risk, this reservation is likely to change.

Interdisciplinary cooperation

The ^{90}Y-ibritumomab tiuxetan regimen is typically administered on an outpatient basis over approximately 1 week. The delivery of ^{90}Y-ibritumomab tiuxetan requires the establishment of new multidisciplinary teams in many hospitals. Such teams are likely to include a haemato-oncologist, nuclear medicine physician or radiation oncologist, nuclear pharmacist, and speciality nurses. The relatively short physical half-life of ^{90}Y (64 h) makes it essential that ibritumomab tiuxetan is radiolabelled at a radiopharmacy or similar immediately prior to use [9].

Although most information about the ^{90}Y-ibritumomab tiuxetan therapy will have been provided by the haemato-oncologist, the nuclear medicine physician, who is responsible for the administration of ^{90}Y-ibritumomab tiuxetan, should provide patients with additional information on radiation therapy and written information describing ^{90}Y-ibritumomab tiuxetan treatment, safety precautions within the week following therapy, anticipated adverse events, and contact telephone numbers [10].

Selection of patients suitable for treatment with ^{90}Y-ibritumomab tiuxetan typically remains with the haemato-oncologist and is an important step in optimizing the benefits of RIT for patients. In some countries such as Germany, where office-based haemato-oncologists are the norm, there may be concerns about 'losing' patients to another speciality with a consequent loss of income by the original haemato-oncologist. This can sometimes lead to haemato-oncologists trying all other therapies at his or her disposal first and only when these options have failed referring patients for treatment with ^{90}Y-ibritumomab tiuxetan. Reassurance that the patient who has received therapy with ^{90}Y-ibritumomab tiuxetan will be directed back to their referring haemato-oncologist should help to address this concern. Such reassurance should also encourage the referral of more patients who have received fewer prior treatments and in doing so maximize the significant therapeutic benefits that ^{90}Y-ibritumomab tiuxetan is able to provide.

Reimbursement and cost-effectiveness

The European reimbursement situation in relation to the approved use of radioimmunotherapies needs further improvement. In this context it is unacceptable that an approved and efficacious radioimmunotherapy in follicular non-Hodgkin's lymphoma is sometimes reimbursed at only a small fraction of the treatment cost, as is currently the case in systems awaiting a specific RIT DRG code, such as Germany and Italy. Growing pressures on health care budgets worldwide have led to an increasing interest in the use of health economics data to support the added value of new therapies in terms of both outcomes and cost and such data is available for ^{90}Y-ibritumomab tiuxetan demonstrating cost-effectiveness relative to rituximab.

Gabriel *et al.* [11] compared the cost-effectiveness of ^{90}Y-ibritumomab tiuxetan versus rituximab (4-dose scheme) for outpatient treatment in Germany (based on a price year of 2004) in patients with relapsed or refractory follicular NHL. In this analysis drug acquisition costs in addition to physician fees for drug application and resource utilization due to adverse events data were considered. Cost-effectiveness was determined as cost per year in remission by relating costs to the overall response rate and duration of response; cost per disease-free year was based on complete response rate and duration of response of complete response patients. The conclusion of the analysis was that although the total cost of the ^{90}Y-ibritumomab tiuxetan regimen was higher (€19 567 vs. €9756), the cost per year in remission (€14 862 vs. €16 967) and in particular cost per disease-free year (€22 235 vs. €80 077) were clearly in favour of ^{90}Y-ibritumomab tiuxetan. This conclusion was driven largely by the superior response rates and in particular complete response rates for ^{90}Y-ibritumomab tiuxetan over rituximab monotherapy. Also in a recent Dutch study, Thompson and van Agthoven estimated the incremental cost-effectiveness of ^{90}Y-ibritumomab tiuxetan compared with rituximab based on either a 4-dose or an 8-dose scheme [12]. The mean total costs were estimated as follows: ^{90}Y-ibritumomab tiuxetan €16 345, rituximab 4-dose scheme €9510 and rituximab 8-dose scheme €19 020. The expected number of months in remission per patient treated were 14.4 months for ^{90}Y-ibritumomab tiuxetan, 11.4 months for the rituximab 8-dose scheme and 6.2 months for the rituximab 4-dose scheme, resulting in a mean cost per month in remission for ^{90}Y-ibritumomab tiuxetan of €1138, followed by €1544 for the rituximab 4-dose scheme and €1674 for the rituximab 8-dose scheme. The price year of this Dutch study for all resources valued, except the ^{90}Y-ibritumomab tiuxetan product, was 2001 and, unlike for Germany,

value added tax does not need to be added to the wholesale price of the product in the Netherlands, thus the lower overall treatment cost in this market.

Since the total cost of a ^{90}Y-ibritumomab tiuxetan treatment is derived mainly from the cost of the therapy itself (rituximab pre-dosing, ibritumomab tiuxetan and ^{90}Y) and the product price is not subject to major differences across the world (except the USA), the cost of a treatment with ^{90}Y-ibritumomab tiuxetan hardly varies from country to country. In contrast, the cost of therapies that ^{90}Y-ibritumomab tiuxetan could potentially replace may vary more, so that the relative cost-effectiveness of ^{90}Y-ibritumomab tiuxetan could be more favourable in countries with higher wage rates for health professionals. For example, if we compare a high-income country such as Germany with a European country that is associated with a lower per capita national income such as Bulgaria, and compare the cost of ^{90}Y-ibritumomab tiuxetan and CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) in each environment, we would clearly see differences. In this example, CHOP in Germany is reasonably expensive for such an old chemotherapy (around €10 000), whereas in Bulgaria it may be about half this figure. This is because the cost of hospital and outpatient visits and health professional time required to provide all chemotherapy infusions is relatively low in Bulgaria by comparison. In addition, there are cheap generics manufactured by eastern and often state-run companies, which further reduce costs when compared to Germany.

Although there are various treatment alternatives in follicular non-Hodgkin's lymphoma, only a few studies have so far focused on their costs [13]; these include Sweetenham *et al.* [14], Herold *et al.* [15] and van Agthoven *et al.* [16].

The most reliable source of data to date is from a patient level costing study by van Agthoven *et al.* [16]. In this study, direct health care costs associated with the most commonly prescribed treatments for indolent follicular NHL in the Netherlands were assessed. The treatments evaluated included allogeneic and autologous stem cell transplantation, chlorambucil, CVP, CHOP, fludarabine, radiotherapy, rituximab, and interferon-α maintenance treatment. The authors reported that in relation to costs only, allogeneic and autologous stem cell transplantation were the most expensive treatments identified (mean per patient overall cost impact until first discharge: €45 326 and €18 866, respectively, including the costs of the initial procedure and up to 10 days post-procedure only), compared to fludarabine costing €10 651, rituximab (4-dose scheme) costing €10 628 and CHOP costing €7547. By contrast, classical NHL treatments were found to be the least expensive therapies (CVP: €5268; radiotherapy: €4218; chlorambucil: €2476). In this study only the mean per patient cost was assessed. The relative cost-effectiveness of each therapy was not addressed. The provided data are, however, important for future cost-effectiveness calculations in the context of new treatment options such as combined chemo-immunotherapy or combined chemo-radioimmunotherapy as initial therapy options.

Conclusion

New clinical technologies such as radioimmunotherapy need to be further integrated into the management pathway of patients with follicular non-Hodgkin's lymphoma. RIT and ^{90}Y-ibritumomab tiuxetan, in particular, offer significant advantages to both the haemato-oncologist and the patient including long response durations, a favourable safety profile and the convenience of a treatment that (local radioprotection laws permitting) can be administered on an outpatient basis over two single clinic visits and within 1 week. In addition, for patients, this benefit comes without the alopoecia, mucositis, or severe nausea or vomiting often accompanying conventional chemotherapy. Furthermore, the cost-effectiveness data for ^{90}Y-ibritumomab tiuxetan reviewed in this editorial provide convincing evidence in favour of the added value of ^{90}Y-ibritumomab tiuxetan in terms of cost per month in remission or cost per disease-free month despite higher initial product acquisition costs. Good collaboration between the haemato-oncologist and nuclear medicine physician and the referral of patients suitable for treatment are likely to maximize the outcomes RIT can provide for the patient with follicular non-Hodgkin's lymphoma.

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