What are the indications for postchemotherapy retroperitoneal lymph node dissection?

Platinum combination chemotherapy has dramatically altered the survival curves for all stages of testicular cancer. We entered our first patient in August 1974 on our phase II trial of the then experimental drug, cisplatin, combined with vinblastine + bleomycin (PVB) [1]. This study immediately transformed metastatic testicular cancer from a highly fatal disease to a model for a curable neoplasm, as over 50% of our 47 patients on our first PVB trial achieved durable complete remission with chemotherapy alone or with postchemotherapy retroperitoneal lymph node dissection (RPLND) (5 patients). This single-institution phase II trial led to the approval by regulatory agencies of cisplatin as a component of combination chemotherapy, despite never having been subjected to the rigors of a phase III trial. Subsequent PVB studies, carried out mainly at Indiana University and through the American Co-operative Groups and in Europe, demonstrated the reduction of the vinblastine dose and elimination of 2 years of maintenance vinblastine would mitigate acute toxicity without compromising cure rates. A subsequent phase III trial determined that the substitution of etoposide (BEP) for vinblastine ameliorated the neuromuscular toxicity and improved the cure rate. PVB became a historical footnote with the completion of this randomized trial in 1984. Further reduction in acute morbidity was accomplished in patients with good risk metastatic germ-cell tumors with the demonstration that equivalent durable remission were achieved with BEP×3 over 9 weeks compared with the control arm of BEP×4 administered over 12 weeks. The high cure rate of metastatic testicular cancer represented one of the landmark achievements in oncology [2].

Testicular cancer is uniquely chemosensitive and chemocurative. Perhaps, less well appreciated is the high success rate of RPLND in this patient population. There is a higher cure rate with presence of nodal metastases with RPLND as initial therapy or following cisplatin combination chemotherapy than any other epithelial cancer.

What is the role of RPLND in the modern cisplatin era? In this issue of the Annals of Oncology, Ravi et al. interrogate the literature as well as their own data from Dana Farber addressing the role of postchemotherapy RPLND in patients with normal size (<1 cm) nodes on CT scan [3]. This editorial will also expand the query as to the value of RPLND for patients presenting with clinical stage I–II disease and for situations with >1 cm nodes remaining postchemotherapy.

clinical stage I nonseedominatous germ-cell tumors

The majority of patients with clinical stage I non-seminomatous germ-cell tumors (NSGCT) will be cured with orchiectomy alone. However, there is a higher probability of occult metastatic disease if there was vascular invasion in the orchiectomy specimen. A recent international panel of authors, in a Comments and Controversies piece, concluded that surveillance is the preferred approach for clinical stage I testicular cancer [4]. However, as is often the case in science, there was not a unanimity of congruence, as an accompanying editorial still championed the role of RPLND, especially for NSGCT patients with vascular invasion [5].

clinical stage II NSGCT

In our opinion, as well as that of other expert centers, RPLND is the preferred option for clinical stage II disease if the node in question is <3 cm [6, 7]. An exception to this would be patients with rising serum human chorionic gonadotropin (hCG) or alphafetoprotein (AFP), as they are best treated with chemotherapy [8, 9].

postchemotherapy RPLND in NSGCT with >1 cm nodes

There is no controversy about the need for RPLND in this setting, preferably carried out at a tertiary center by an experienced urologic oncologist [10, 11]. A postchemotherapy CT scan merely depicts the size and location of nodes, not the pathology (germ-cell cancer, teratoma, or necrosis). There is no role for subsequent induction nor salvage chemotherapy in this setting in the absence of a rising hCG or AFP.

salvage surgical RPLND

Traditionally, postchemotherapy RPLND is reserved for patients with normal serum hCG and AFP. However, selected patients who are chemorefractory with rising markers, but disease confined to abdominal nodes, can be salvaged with RPLND. Murphy et al. first reported our results from Indiana University. Ten of 48 (21%) patients were rendered disease-free and remain with no progression postoperatively. Best results were achieved with rising AFP (as opposed to hCG) and disease confined to the retroperitoneum [12]. Similar results have been confirmed by other centers [13].
postchemotherapy RPLND for patients with subcentimeter nodes

Ravi et al. have provided excellent data, information, and guidelines in this issue of the *Annals of Oncology*, by carefully analyzing meta-analysis of patient outcomes as published in manuscripts and abstracts, as well as adding an additional 47 patients from their own institution [3]. Our standard approach has always been surveillance and we have never endorsed RPLND in this setting [14]. However, other institutions have implemented postchemotherapy RPLND, regardless of whether CT scan reveal > or <1 cm residual masses [15–18]. Three of these four references were only published as abstracts. The Oldenburg paper assessed 87 patients with residual tumors <2 cm, including 54 < 1 cm. There were 5 findings of germ-cell cancer and 11 mature teratoma [15]. Some of these patients were treated with carboplatin, an inferior platinum compared with cisplatin.

On meta-analysis, 588 patients were accumulated who underwent postchemotherapy RPLND, with findings of active cancer in 4% and teratoma in 24%, respectively. It is unknown whether microscopic teratoma in these series is biologically inert and incapable of growth.

We recently published our results in 141 patients who underwent surveillance with a median follow-up of 15.5 years. Twelve of 141 (9%) relapsed with 8 of these 12 NED with subsequent surgery or salvage chemotherapy. Only six relapses were in the retroperitoneum, and four of these six are currently NED [19]. Similar results were reported by Kollmannsberger in 161 patients, but with shorter follow-up [20].

The series by Ravi et al. included 47 patients undergoing surveillance with a median 5.4 year follow-up. Three of 47 relapsed, but all are currently alive with further treatment [3]. Overall, in their analysis, only 5% of 455 men who underwent surveillance relapsed with a retroperitoneal relapse rate of 3%.

These data are compelling to avoid postchemotherapy RPLND in this patient population. What, if any, are the arguments in support of RPLND?

- The occasional 3%–5% relapse rate in the abdomen might have been prevented and thus avoided salvage chemotherapy or mortality by performing RPLND. The data do not support this philosophy. There will never be a zero relapse rate, even in patients undergoing RPLND.
- Serial CT scans are expensive and may be carcinogenic. In our Indiana series, we did not perform subsequent CT imaging after achieving a CR.

In summary, we agree with the conclusions of Ravi et al. that surveillance is a reasonable strategy and avoids an RPLND in ~97% of men cured with chemotherapy alone. Postchemotherapy RPLND is not an innocuous procedure with a 20%–30% complication rate [21, 22] and anejaculation in 20% of patients [23]. Postchemotherapy RPLND in patients with complete remission would never be approved by any regulatory agency if it were evaluated as a drug or device, as the data does not support improved outcomes or less toxicity. In my opinion and based upon data presented by Ravi et al., there is little or no indication for performing postchemotherapy RPLND in patients with subcentimeter nodal findings.

disclosure

The authors have declared no conflicts of interest.

references

Actual developments in European regulatory and health technology assessment of new cancer drugs: what does this mean for oncology in Europe?

Introduction

The incidence of cancer has been estimated at 11 million cases per year with a global prevalence of 25 million cases, and the World Health Organisation (WHO) has predicted that within the next decade these figures could increase up to 50%, reaching 15 million new cases per year by 2020 [1, 2]. In Europe, there were an estimated 3.2 million new cases of cancer and 1.7 million deaths from cancer in 2008 [2, 3]. As such, there is a current and growing requirement for more emphasis on cancer prevention, research, therapy in general and better targeted anticancer drugs. Rapid licencing and market availability of innovative, more effective oncology drugs are also a necessity.

Inevitably, health care policy makers have to balance between the infinite level of healthcare demands and their finite healthcare resources. This means that oncology drugs have to be assessed not only on their clinical merit, but also on their cost-effectiveness in comparison with currently available alternative therapies. Currently, this system involves input from two different bodies which increases not only the workload associated with drug development, but also the costs. Most EU member states have delegated these so called relative efficacy, relative effectiveness and cost-effectiveness assessments to dedicated health technology assessment (HTA) agencies. Despite commonalities in scope of the assessments conducted by regulatory agencies and HTA bodies, the applied evidentiary and analytical standards, extrapolations from the underlying clinical evidence base as well as scientific value judgements for the same drug differ substantially between the regulatory and HTA agencies [4, 5].

The current system—status and limitations

different assessments by regulators and HTA bodies

Under the current system, new oncology drugs in the EU are assessed under a centralised procedure by the European Medicines Agency (EMA) in the network of over 40 regulatory agencies from all Member States [6]. Based on the opinion of EMA’s Committee for Medicinal Products for Human Use, the European Commission decides on granting a European marketing authorisation (European MA), which applies to all EU member states. But, because of the various healthcare systems in the EU member states and the strong subsidiarity principle in the field of health care, each member state negotiates on drug price, reimbursement status and allocated funding independently in light of different healthcare system priorities and affordability. These decisions are made on a national or even regional level and usually are based on a formal assessment of the product by HTA bodies. Examples of HTA bodies are the National Institute for Health and Clinical Excellence in the UK, the Haute Autorité de Santé in France and the Institute for Quality and Efficiency in Health Care in Germany. The principles underlying HTA have been described elsewhere [4, 5, 7].

It is important to note that even if a European MA has been granted, this does not imply that the product will be available to patients everywhere in the EU. If public reimbursement is declined based on the negative result of the assessment by the HTA bodies and corresponding payer decisions, the vast majority of patients will not be able to afford the product.

evidence requirements of regulators

(See supplementary file S1, available at Annals of Oncology online.)

evidence requirements of HTA bodies

(See supplementary file S1, available at Annals of Oncology online.)

different approaches across Europe

The approaches to HTA vary across different EU countries with regards to evaluative perspective (payer versus societal), the scope of assessments, and more specifically the use of informal or formal cost-effectiveness assessments and methodology as cost per quality of life year gained (QALY) versus other methods, modelling techniques and discounting, and budget impact analysis.

In Germany, for example, drugs are usually available for reimbursed use as soon as European MA is granted. In 2011, the act for restructuring pharmaceutical market statutory health insurance (AMNOG) was introduced in Germany, giving the