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The EORTC Genito-Urinary Tract Cancer Group: 25 years of achievements and future strategies

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Abstract

The European Organisation for Research and Treatment of Cancer (EORTC) Genito-Urinary (GU) Tract Cancer Group celebrates 25 years of activity in 2001. The Group has developed an intense research activity carrying out phase II and phase III clinical trials in prostate, bladder, renal, penile and testicular cancers. It is one of the most active groups within the EORTC, entering more than 1200 new patients in its trials in 2001. In its trials, the EORTC GU Group also focuses on quality control, quality of life and uro-pathology. Besides collaboration with other EORTC groups, the GU Group is very actively collaborating with international organisations. Currently, several large phase III studies are conducted in collaboration with European and North American organisations. For the next few years, the Group is committed to develop projects aimed at testing new drugs and therapeutic strategies and increasing the collaboration between basic science and clinical practice.

Keywords: Genito-urinary tumours; Randomised trials; Prostate cancer; Bladder cancer; Germ cell cancer; Kidney cancer; Quality of life

1. Introduction

The European Organisation for the Research and Treatment of Cancer (EORTC) Genito-Urinary (GU) Group was founded in 1976 and thereby celebrates 25 years of activity in 2001. The interest of the Group in the early years was mainly focused on phase III studies. After the initial period of its activity (1976–1981), the GU Group started to develop an intense research activity recruiting 1645 patients in 17 protocols from 1982 to 1984. Thereafter, the Group also conducted an increasing number of phase II and feasibility studies along with the phase III studies. In 1995, the Group accrued for the first time in its history more than 1000 patients in one year. In 2000 the GU Group was the most active group within the EORTC Treatment Division, entering more than 1200 new patients in its trials.

From its very beginning, the group has adopted a multidisciplinary strategy, welcoming the collaboration of radiation oncologists, medical oncologists and pathologists. In fact, any investigator interested in urogenital oncology is welcome to join the Group. The GU Group currently has about 200 members throughout Europe: urologists, radiation oncologists, medical oncologists, pathologists and experts in other disciplines. Some other investigators outside Europe, such as Israel, are also members of the GU Group.

The EORTC Genito Urinary Tract Cancer Group carries out phase II and phase III clinical trials in prostate, bladder, renal, testicular and penile cancer. Trials are carried out by Disease Oriented Groups (DOGs). Four committees (Chemotherapy, Quality control, Quality of Life and Uro-pathology) support the DOGs. In collaboration with the EORTC Data Center Quality of Life Unit and the EORTC Quality of Life Study Group, the GU Group Quality of Life Committee has developed specific modules for prostate and superficial and invasive bladder cancer [1]. These modules have been translated and validated in 17 different languages. The GU group was also the first clinical group within the EORTC to emphasise the importance of professional and motivated data management to achieve high quality in clinical trials, setting up a specific GU data managers' and research nurses' group that meets regularly.

Besides very productive collaboration with other EORTC groups, in particular the Radiotherapy Group, the GU Group is also very actively collaborating with other international organisations. The EORTC GU

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Group participates on a regular basis in the meeting of the 'Global GU Group', sharing and discussing new ideas with other international groups. Currently, several large phase III studies are conducted in collaboration with the most active European (British MRC, French FNCLCC) and North American (NCIC, ECOG, SWOG, RTOG) organisations.

2. Achievements and new studies

A number of important achievements have been made during the 25 years of activity of the GU Group. These serve often as the basis to test new hypotheses and launch new trials. A short list sorted by disease site follows.

2.1. Prostate cancer

Several trials have been undertaken in metastatic disease [2]. Two studies have contributed to the still-open debate about whether maximal androgen blockade is really beneficial in advanced prostate cancer. The group contributed to the further definition of the prognostic factors, underscoring that variations in the malignant behaviour of prostate cancer are larger than the possible benefits of hormone therapy [3]. This finding could explain the conflicting results with MAB or simple castration reported by the EORTC GU Group and others.

A study carried out with the Radiotherapy Group has definitively demonstrated that, for patients with locally advanced disease, the association of hormonal treatment with external beam radiotherapy is more efficacious than radiotherapy alone [4]. Another large study investigating the effect of immediate versus delayed hormone therapy is pending final analysis.

From the early years, the GU Group has paid attention to the quality of life of cancer patients. Particular attention has been focused on the quality of life of prostate cancer patients and some relevant papers on this subject have been published [5]. Among others, it is worth underlining the current EORTC GU Group participation in an international trial co-ordinated by SWOG assessing the value of continuous versus intermittent therapy for metastatic patients.

Recently, new studies have been launched for prostate cancer patients. A feasibility study, preceded by a quality control survey, aims to assess the value of surgical approach for selected T3 cancer patients. A large phase III trial is comparing the value of early or delayed step-up/step-down hormonal therapy for patients not receiving local treatment with curative intent. Currently, the GU group is also considering new treatment options for patients with metastatic disease or at high risk of developing bone metastasis that may be developed in new study protocols in the next few months.

2.2. Superficial bladder cancer

Thanks to its large database of more than 4000 superficial bladder patients randomised in several phase III trials over 25 years, the GU Group was able to define the main risk factors in superficial bladder cancer [6]. Stage, grade and the presence of *in situ* carcinoma (Cis) are predictive factors for invasion, whereas the number (multiplicity) of tumours, the prior recurrence rate and the tumour size are predictive for recurrence. A meta-analysis concluded that intravesical chemotherapy delays superficial tumour recurrence, but does not prevent progression to muscle invasive bladder cancer and has no influence on survival [7].

Several major findings have been provided to urologists by the GU studies on superficial bladder cancer: (a) intravesical chemoprophylaxis after trans-urethral resection (TUR) of bladder lesions delays time to future recurrence compared with TUR alone; (b) intravesical BCG is superior to intravesical epidoxorubicin in delaying recurrence for patients with intermediate and high-risk tumour and Cis; (c) for single tumours, even a single instillation of a chemotherapeutic agent is sufficient to exert a prophylaxis; (d) in low- and medium-risk tumours, bladder mapping can be avoided because it rarely provides useful indications for further treatment; (e) pathology review is required only in high-grade lesions; (f) the quality of endoscopic surgery has a great influence on the recurrence rate and patterns in superficial bladder cancer.

A large four-arm randomised trial comparing long- and short-term installations of full versus one-third dose of BCG in intermediate and high-risk papillary tumours will be closed to patient entry in 2002. A new trial has been recently launched to assess the efficacy of BCG alone or combined with MMC for patients with Cis. The innovative approach of chemo-resection to spare trans-urethral resection in a high percentage of patients presenting with a single superficial tumour will be tested in a large phase III study that will be opened in 2002.

2.3. Advanced bladder cancer

The MRC together with the EORTC GU Group launched and co-ordinated the biggest study of neo-adjuvant chemotherapy in locally advanced bladder cancer [8]. Centres all around the world collaborated in this study. Final conclusions are still pending, but should be available in 2002.

Three new trials have been recently opened for locally advanced and metastatic patients. Two trials are comparing different chemotherapy regimens in inoperable advanced or metastatic patients, respectively fit or unfit to receive cisplatin- based chemotherapy. A large intergroup trial will try to answer the open question about the value of immediate versus delayed chemotherapy after radical cystectomy in locally advanced patients.

2.4. Kidney cancer

The GU Group has been and still is deeply interested in kidney cancer clinical studies. A large-scale study established that, in organ-confined disease, extended lymph-node dissection does not add any benefit to nephrectomy performed only with local lymph-node dissection [9]. The Group also collaborated in a study carried out in the USA which concluded that, in metastatic disease, palliative nephrectomy added to interferon is more beneficial than interferon therapy alone [10]. The GU Group will join in the near future a Medical Research Council (MRC) phase III trial comparing in metastatic patients monotherapy with interferon to triple combination therapy.

2.5. Penile cancer

In the near future, a phase II trial will be launched testing the use of irinotecan for advanced disease in this rare tumour site.

2.6. Germ cell cancers

The GU Group has had a continuous collaboration with the EORTC Early Clinical Studies Group particularly in the field of testicular cancer, and a number of new drugs have been tested. The GU Group also works intensively with other co-operative groups, in particular with the MRC Testicular Cancer Working Party [11]. For instance, alternating PVB and BEP, cisplatin + vincristine + ifosfamide regimens were extensively investigated in metastatic patients. Comparisons of BEP with BE-Carboplatin, of four cycles of BEP versus four cycles of VIP and of induction–sequential BOP/VIP-B with BEP/EP were also carried out. In good prognosis metastatic patients, it was proved that three BEP courses are equivalent to three BEP-EP courses.

A phase II/III trial is currently ongoing to confirm the results of a phase I/II study that assessed the feasibility of the addition of paclitaxel to BEP (T-BEP) in patients with intermediate- or poor-prognosis germ-cell cancer [12].

Quality of life has been extensively assessed to evaluate the benefit of new treatment strategies in this young patient population [13].

3. Future strategies

Both medicine in general and cancer clinical research in particular have seen an unprecedented rate of development during the last century. At the beginning of the twentieth century, the art of medicine was effectively in 'prehistoric times'. Not everyone is aware, for instance, that the Cancer Research Laboratories of the Middlesex Hospital were founded in London in 1900, starting a new era in cancer research, or that penicillin was discovered in 1928, leading to a revolution in clinical practice, or that PSA was identified only in the 1980s.

In more recent times, the evolution of oncology and urology has registered an even greater acceleration. New discoveries in molecular research, genetics, etc., have contributed greatly to that evolution. The interaction between basic science and clinical practice and the increasingly global circulation of scientific information render the analysis and interpretation of new data very complex. The translation of new knowledge into practice in some instances, therefore, can be difficult or at least delayed.

The EORTC GU Group has identified four major objectives for the next few years. These are: testing new drugs; testing new therapeutic strategies; increasing the collaboration between basic science and medical practice in uro-genital cancer; and collaboration in creating central tissue banks.

3.1. Testing new drugs

Progress in the medical treatment of uro-genital cancer is clearly related to the availability of new, more efficacious drugs, which are constantly being developed and are preliminarily tested by the appropriate EORTC Groups. The EORTC Early Clinical Studies Group (ECSG) to become the New Drug Development Group (NDDG) has the task of studying new drugs in phase I/II clinical trials. The ECSG is currently conducting a phase II of new oral topo-isomerase inhibitor in urothelial tract tumours and has opened a phase II trial of a new generation anthracycline in hormone-relapsed prostate cancer. The GU Group plans to further increase collaboration with the NDDG. A subsequent step is the comparison of promising new drugs with standard treatments.

3.2. Testing new therapeutic strategies

In the treatment of uro-genital cancer, more and more new strategic approaches are used. The most conspicuous example is represented by new surgical techniques. The GU Group plans to explore the therapeutic potential of some of these promising strategies and also to use established techniques with new indications. Examples of these projects are the assessment of radical prostatectomy in locally advanced prostate cancer and a study comparing laparosopic radical prostatectomy with standard open surgery.

3.3. Increasing the collaboration between basic science and medical practice in uro-genital cancer

One of the difficulties encountered in modern times is the slow translation of the achievements of basic research into practice. In particular, there is a delay in applying suggestions arising from basic research into

routine practice. Presently, the EORTC is supporting the general concepts related to translational research and the GU Group is involved in this field. The GU Group has an active Pathology Committee which is already working in that direction and this activity will be enhanced in the near future. The possibility of close collaboration with the International Bladder Cancer Network is also being considered.

3.4. Collaboration in creating central tissue banks

The creation of a central Tissue Bank is among the EORTC projects. This Bank, located within the EORTC Data Center, will be both 'virtual' (consisting of the storage of pathological tissue images in order to make reference patterns available for consultation) and 'real' (tissue blocks or pathological slides will be stored and, when necessary, re-cut for special exams, research or consultation). Two new bladder cancer protocols have been already selected for the pilot phase of this project. A new project, similar to the central Tissue Bank, will involve the centralisation of pathological slides related to prostate biopsies negative for cancer from patients in which prostate cancer is clinically suspected. This project, due to start within the next few months, should allow the identification of the factors predicting the negative findings. A field of possible future investigation could be the collection of prostate specimens with prostatic intraepithelial neoplasia (PIN) to study its characteristics.

4. Conclusions

It can be confidently predicted that, in the coming years, basic, biochemical and biological research will provide doctors with a large number of new therapeutic tools. Identifying and testing these new clinical avenues is considered the major task for the EORTC GU Group.

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