The EORTC Genito-Urinary Cancers Group: 35 years of achievements and future strategy

R. Sylvester, L. Collette, A. Bex, N. Clarke, C.N. Sternberg, B. Tombal, on behalf of the EORTC Genito-Urinary Cancers Group

Keywords:
Urothelial carcinoma of the bladder
Prostate cancer
Renal cell carcinoma
Testicular cancer
Randomized clinical trials

ABSTRACT

Founded 35 years ago, the European Organisation for Research and Treatment of Cancer Genito-Urinary Cancers Group (GU Group) has carried out a total of 99 phase I, II and III clinical trials in the fields of bladder, prostate, kidney, testicular and penile cancer. Meta-analyses have answered clinically important questions that the individual studies could not answer by themselves.

From its very beginning, the GU Group has adopted a multidisciplinary approach, with collaboration among urologists, medical oncologists, radiation oncologists, pathologists and biostatisticians. It has also had a very successful collaboration with the EORTC Radiation Oncology Group and with national organizations such as the UK Medical Research Council.

The results of their work, which remain standards in the field today, have directly led to major worldwide improvements in day to day clinical practice and have been incorporated into treatment guidelines such as those of the European Association of Urology.

The group's intention is to build on this important legacy and to continue to develop and recruit to the multicenter, international randomized studies that have been their hallmark. Their primary aim will be to focus on clinical trials that investigate strategic therapeutic questions and which have the potential to change medical practice and improve our understanding of urologic malignancies. This includes studies with strong translational research components, prospective clinico-genomic and cancer biology/biomarker data and clinical trials addressing rare tumor types. To carry this strategy into the future, the contribution of individual clinicians, collaborative cancer trial groups and pharmaceutical companies is of fundamental importance.

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the GU Group has carried out a total of 99 phase I, II and III clinical trials in the fields of bladder (35 trials), prostate (30 trials), kidney (18 trials), testicular (15 trials) and penile cancer (1 trial). Meta-analyses have also been carried out to answer a number of important questions that the individual studies could not answer by themselves. The work of the GU Group has directly contributed to changes in clinical practice worldwide and has been incorporated into various treatment guidelines such as those of the European Association of Urology (EAU).

From its very beginning, the GU Group has adopted a multidisciplinary approach, as evidenced by the collaboration among urologists, medical oncologists, radiation oncologists, pathologists and biostatisticians. It has also had a very successful collaboration with the EORTC Radiation Oncology Group in conducting large phase III trials in prostate cancer, and with various national organizations such as the UK Medical Research Council for testicular and bladder cancer. An intergroup collaboration with groups funded by the US National Cancer Institute (NCI) in the USA has also been in place.

2. Achievements

Bladder cancer and prostate cancer have each accounted for approximately one third of the studies that the GU Group has conducted. Some of the most important achievements by disease site are summarized below.

2.1. Urothelial carcinoma of the bladder and urinary tract

The GU Group has been active in both non muscle invasive (superficial) bladder cancer and advanced bladder/urinary tract cancer, with trial results and meta-analyses having had a direct impact on day to day clinical practice.

2.1.1. Non muscle invasive bladder cancer (NMIBC)

The GU Group has carried out 11 randomized phase III trials comparing different adjuvant intravesical and oral treatments after transurethral resection of the bladder tumor (TURBT). Together with the EORTC Headquarters, the GU Group has also published four meta-analyses and one combined analysis comparing different adjuvant regimens.

Randomized studies, meta-analyses and combined analyses of the group have shown that:

- Intravesical chemotherapy delays the time to first recurrence after TURBT but not the time to progression.2
- No individual intravesical chemotherapy regimen has been identified as being superior to another (trials 30751, 30782, 30791).3–5
- A single immediate post TURBT instillation of chemotherapy reduces the risk of recurrence by 39%.6,7
- The optimal schedule and duration of intravesical chemotherapy after an immediate post TURBT instillation remains unknown (trials 30831, 30832).8,9
- In intermediate and high risk patients (papillary tumors and/or carcinoma in situ), intravesical BCG is superior to intravesical chemotherapy in delaying the time to recurrence, time to progression and death due to bladder cancer but only when maintenance BCG is given (trials 30845, 30906, 30911).10–13
- Intravesical BCG has more local and systemic side effects than intravesical chemotherapy, however maintenance BCG is not associated with increased long term toxicity (trial 30911).14,15
- Intravesical BCG side effects do not predict its efficacy (trial 30911).16
- No difference in efficacy between BCG strains could be identified.13
- Results of trial 30962 comparing two different BCG doses (full dose versus one third dose) and durations of treatment (one year maintenance versus three years maintenance) in more than 1300 stage TaT1 patients will be available in 2012.

An internationally recognized prognostic factor scoring system (EORTC Risk Tables) based on 2596 patients from seven EORTC studies has been developed to predict a patient’s probability of recurrence and progression using software available on the EORTC website. This unique resource allows the choice of treatment and frequency of follow up to be tailored according to the individual patient’s prognosis.17

The GU Group has demonstrated a large variability in the recurrence rate at the first follow up cystoscopy between institutions.18 These results have highlighted the need for stricter surgical quality control and for pathology review, which is essential for the accurate staging of high risk T1G3 patients.19

The GU Group has thus played a major international role in establishing Level 1 evidence to guide the treatment of patients with NMIBC, leading to major improvements in routine day to day care, especially in establishing a single immediate post TURBT instillation of chemotherapy6,7 and the long-term superiority of BCG to compared chemotherapy12 as cost effective standards. Through this evidence base and the associated EORTC NMIBC risk calculator, the GU Group has played a leading role in the development of the European Association of Urology (EAU) Guidelines for the treatment of this disease, the most expensive of all cancers.20

2.1.2. Locally advanced bladder cancer (muscle invasive)

The long-term results of the EORTC/MRC intergroup randomized study 30894/BA06 have confirmed a statistically significant prolongation of overall survival with cisplatin–methotrexate–vinblastine (CMV) neo-adjuvant chemotherapy, with a reduction of 16% in the risk of death. This study in 976 patients, the largest ever
in locally advanced bladder cancer, has established neo-adjuvant chemotherapy followed by definitive local therapy (radical cystectomy or radiotherapy) as a state of the art treatment for patients with muscle invasive bladder cancer.  

EORTC intergroup study 30994 comparing immediate versus deferred chemotherapy after radical cystectomy is still in follow up. This study, the largest ever randomized study of adjuvant chemotherapy after cystectomy, will provide high level evidence concerning the possible benefit of adjuvant chemotherapy.

2.1.3. Advanced urothelial cancer of the urinary tract (unresectable and metastatic)
In advanced urinary tract urothelial carcinoma, three EORTC randomized studies have been carried out:
• High dose M-VAC with G-CSF was shown to be superior to classical M-VAC with respect to both efficacy and toxicity, thus establishing high dose M-VAC as a standard treatment for advanced disease (trial 30924).  
• The only randomized trial comparing two carboplatin-based regimens in patients unfit for cisplatin has shown that gemcitabine/carboplatin is the preferred regimen based on its favorable toxicity profile (trial 30986).  
• In previously untreated patients, the addition of a taxane to the standard regimen of gemcitabine and cisplatin failed to provide a statistically significant improvement in overall survival, however in a post hoc subgroup analysis, a 19% reduction in the risk of death in patients with bladder as the site of the primary tumor was observed (trial 30987) [J Clin Oncol, in press].

2.2. Prostate cancer
GU group prostate cancer (PCa) studies have led to 128 peer-reviewed publications from 1986 to 2010. Research has focused on the role of hormone therapy in advanced and metastatic PCa and on the benefit of adjuvant external beam radiation therapy (EBRT). Other studies have also investigated new therapies in castration-resistant PCa. Some of the most important studies are summarized in the following.

2.2.1. Metastatic prostate cancer
The group has demonstrated the limited benefit of Maximum Androgen Blockade (MAB) with non steroidal anti-androgens, the lack of benefit of MAB with cyproterone acetate (CPA) and the cardiovascular toxicity of estrogens:
• MAB (monthly goserelin acetate and flutamide) significantly increases progression-free, overall and PCa-specific survival compared to orchietomy (trial 30853), but there was no difference between orchietomy and buserelin combined with CPA, taken either continuously or during only 2 weeks (trial 30843).  
• Study 30805, comparing orchietomy, orchietomy plus CPA, and daily stilboestrol (DES) (1mg) showed no difference in efficacy, but identified the cardiovascular toxicity of DES.  

Prior to study 30805, the very first GU Group trials in patients with either metastatic or locally advanced prostate cancer compared DES to CPA to medroxyprogesterone acetate (MPA) (trial 30761) or to Estracyt (trial 30762). MPA was found to be inferior to CPA and to DES, however there was no difference in efficacy between DES and Estracyt.

Although the MAB studies suggest that flutamide may be superior to CPA, no difference in efficacy was found in metastatic patients with favorable prognostic factors (trial 30892).

In poor-prognosis metastatic prostate cancer, the administration of mitomycin C after orchietomy had significant toxicity, a negative impact on quality of life and decreased overall survival (30893).  

Four randomized studies have been carried out in hormone refractory prostate cancer, studying mitomycin C versus Estracyt (trial 30865), flutamide versus prednisone (trial 30903), strontium chloride versus palliative field local radiotherapy (trial 30921) and satraplatin plus prednisone versus prednisone alone (trial 30972). Only satraplatin appeared to be more effective with acceptable toxicity, leading to further studies.

2.2.2. Locally advanced prostate cancer
The GU Group challenged the conventional wisdom that every advanced PCa patient should be treated immediately with androgen deprivation therapy (ADT). Two important trials studied long-term ADT in men with locally advanced PCa who were unfit for radical treatment:
• Study 30891 compared immediate versus deferred ADT in 985 patients with T0–4N0–2M0 PCa. The overall survival results favored immediate treatment (HR=1.25), seemingly due to fewer non PCa deaths. However neither time to castration-resistant disease, nor PCa-specific survival differed. Further investigations suggested that the greatest benefit of immediate ADT in older patients was seen in those with an initial PSA > 50 ng/ml and/or with a rapid PSA doubling time (<12 months), i.e. in patients who are at a higher risk of dying from PCa, but that older patients with initial PSA < 50 ng/ml and a slow PSA doubling time could be spared the burden of immediate ADT.  

• Study 30846 compared early versus delayed ADT when radical prostatectomy was aborted after finding positive lymph nodes. After 13 years of follow-up, overall and PCa-specific survival on both arms appeared similar, but non-inferiority could not formally be shown.  

Together with the EORTC Radiation Oncology group, the GU Group demonstrated that long-term adjuvant
hormone therapy benefits locally advanced PCa patients treated by external beam radiotherapy (EBRT):

• Study 22863 demonstrated that added to EBRT, 3 years of ADT increased 5-year overall and PCa-survival by 15%. The benefit was maintained at 10 years.32

• Later in the same setting, study 22961 compared 6 months ADT to 3 years ADT and showed a 5% greater 5-year overall survival with the longer ADT regimen.33

The EORTC GU and Radiation Oncology groups also investigated the benefit of adjuvant radiotherapy in patients with adverse pathological factors after radical prostatectomy:

• Study 22911 randomized 1005 men between surveillance and immediate EBRT. The initial reports showed that EBRT significantly improved biochemical and locoregional progression-free survival at 5 years. However with 10 years median follow-up, the study has not shown a benefit in time to metastases or duration of survival.34

The GU Group has thus carried out clinically important, practice-changing prostate cancer studies, the results of which remain referenced standards in the field today.

2.3. Renal cell carcinoma

The GU group has performed 16 studies in kidney cancer, including seven phase III trials comparing different surgical approaches, multimodality treatment concepts integrating surgery and medical treatment and systemic therapies for locally confined and advanced renal cell carcinoma. In addition, a major phase III trial is ongoing to investigate the sequence of cytoreductive nephrectomy and systemic therapy in metastatic renal cell carcinoma.

Landmark randomized studies of the GU group have shown that:

2.3.1. For locally confined kidney cancer

• Nephron sparing surgery is safe and not inferior to radical nephrectomy in patients with a solitary, \( \leq 5 \text{ cm} \) T1–T2 N0 M0 renal cell carcinoma (trial 30904).35

• After proper preoperative staging, the incidence of unsuspected lymph-node metastases is low (4.0%) and a complete node dissection in conjunction with radical nephrectomy does not improve survival (trial 30881).36

• Adjuvant combination therapy with interferon (IFN) alfa, interleukin-2, and 5-FU is associated with significant toxicity and does not improve overall or disease-free survival in patients at high risk of progression after nephrectomy (trial 30955).37

2.3.2. For metastatic kidney cancer

• Progression-free and overall survival for progressive patients treated with IFN-alpha-2a plus 13-CRA were significantly longer compared with patients on IFN-alpha-2a alone (trial 30951).38

• Cytoreductive radical nephrectomy before IFN-based immunotherapy substantially delays time to progression and improves duration of survival of metastatic patients with a good performance status (trial 30947). These results were consolidated in a combined analysis of data from this study and data from the SWOG.39,40

• Combination therapy with IFN alfa-2a, interleukin-2, and fluorouracil does not improve overall or progression-free survival compared with IFN alfa-2a alone (trial 30012).41

• Combination IFN gamma and IFN alpha 2-c is not more effective than IFN alpha 2-c alone (trial 30885).42

The GU group has undertaken large randomized phase III trials in the field of renal cancer, generating Level 1 evidence to facilitate management in this field. This evidence base has enabled the development and international dissemination of techniques establishing the place of nephron sparing surgery, lymph node dissection and cytoreduction in renal cancer surgery and has determined the effectiveness of combination immunotherapeutic regimens in metastatic disease.

2.4. Testicular cancer/germ cell tumors

Three trials were initially carried out in non seminomatous germ cell tumors (NSGCT):

• Trial 30795 compared high-dose to low-dose vinblastine in cisplatin–vinblastine–bleomycin (PVB) induction chemotherapy.43

• In trial 30824, four cycles of bleomycin, etoposide and cisplatin (BEP) were compared to four cycles of EP in good-prognosis patients and four cycles of BEP were compared to alternating PVB/BEP in poor-prognosis patients.44,45

• Trial 30873 compared four cycles of BEP to four cycles of VIP in intermediate-prognosis patients.46

A number of germ cell tumor trials have been carried out together with the UK Medical Research Council (MRC):

• In poor-prognosis patients, six cycles of sequential BOP/VIP-B were compared to BEP/EP with and without G-CSF (trial 30895).47,48

• In good-prognosis patients, four cycles of BEP were compared to BEC (carboplatin) (trial 30896).49

• Trial 30941 attempted to show the non-inferiority of 3 versus 4 cycles of BEP and a 3-day versus a 5-day schedule of BEP in good-prognosis patients.50,51

The following lessons have been learned from these studies:

In good-prognosis patients, BEP is more effective than EP but is associated with more pulmonary and neurotoxicity. Carboplatin is inferior to cisplatin and cannot replace it. Treatment can be given in 3 cycles rather than in 4 and in 3 days rather than in 5 days.
In intermediate- and poor-prognosis patients, other treatment regimes such as PVB/BEP, VIP, and BOP/VIP-B were not shown to be more effective than BEP but were more toxic, especially in relation to hematological toxicity. G-CSF improved dose delivery but not efficacy and hence its use with BEP/EP is not justified.

More recently, the results of two important randomized studies have become available:

- A randomized phase III study of sequential high-dose cisplatin/etoposide/ifosfamide plus stem cell support versus BEP in patients with poor-prognosis germ cell cancer (trial 30974) has been completed. This study showed that high-dose chemotherapy did not improve the outcome in poor-prognosis patients.

- A randomized phase II/III study of paclitaxel-BEP versus BEP in patients with intermediate prognosis germ cell cancer (trial 30983) showed that there was no significant difference in the primary endpoint, the duration of progression free survival, based on an intent to treat analysis.

The GU Group also contributed to MRC trials that assessed the optimal adjuvant treatment for stage I seminoma patients. One trial (MRC TE18/EORTC 30942) was designed to compare the efficacy and acute and long-term morbidity of standard radiotherapy with 30 Gy in 15 fractions versus 20 Gy in 10 fractions whereas the other trial (MRC TE19/EORTC 30982) assessed the non-inferiority of single-agent carboplatin to radiotherapy. Optionally, patients allocated radiotherapy within TE19 could be randomly assigned between 20 and 30 Gy, with the intent that these patients could also contribute to the question addressed by TE18 at a later date. TE18 showed that 20 Gy of irradiation is unlikely to produce relapse rates more than 3% higher than the standard 30 Gy. Reductions in morbidity with shorter treatment enable patients to return to work more rapidly.

Trial TE19 has shown the non-inferiority of a single course of carboplatin at preventing relapses compared to radiotherapy in the treatment of stage I seminoma, with a reduced risk of second cancers. A combined analysis of TE10, TE18 and TE19 has provided support for the use of either radiation therapy or carboplatin as adjuvant treatment for stage I seminoma.

Together with the MRC, the studies of the GU Group have been instrumental in defining the optimal treatment in testicular cancer patients. To date, it has not been possible to find a therapeutic regimen which is superior to BEP for NSGCT.

3. Future perspectives and strategy

The GU Group has made a significant and internationally important contribution to the practice of Urological Oncology. It is the group’s intention to build on this important legacy in the future and to continue to develop and recruit to multi-center, international randomized studies that have been the hallmark of this clinical trials group. The group’s primary aim will be to focus on clinical trials that investigate strategic therapeutic questions and which have the potential to change medical practice and to improve our understanding of urologic malignancies. To this end the GU Group will follow the general EORTC Scientific Strategy, encompassing design and recruitment to phase III academic trials aimed at changing the standard of care, studies with strong translational research components, including prospective clinicogenomic and cancer biology/biomarker data and clinical trials addressing rare tumor types.

In designing and coordinating clinical trials, current and emerging difficulties need to be acknowledged, most notably the increasing breadth of the statutory legislation required for pan-European studies. The burgeoning requirements for patient information, trial documentation and the differences in regulations regarding sample collection for translational research bring genuine difficulties for trial groups and clinicians alike. The corollary of this is that the complexities, cost and time taken to develop and run modern RCTs have substantially increased. Faced with these difficulties, it would be easier for clinicians to take the path of least resistance and accept the status quo. However, these issues require a stiffer resolve and the importance of attempting to answer the questions at hand is exemplified in this overview, where the influence of well-conducted RCTs on modern day practice is clear to see. RCTs run by academic groups such as the EORTC GU Cancers Group must remain the keystone in the development of modern cancer care. This academic approach is the most appropriate for evaluating optimal new therapies, their sequencing, targeting and their combination with other agents.

The future multidisciplinary ethos of the GU Group will continue to involve urologists, medical oncologists and radiotherapists working in tandem with pathologists, radiologists, translational scientists and biostatisticians. Planned collaborations will incorporate biomarker and imaging consortia in both prospective data gathering and retrospective archive analysis. This approach is reflected in translational research programs currently being integrated into GU Group trial 30073, investigating the sequencing of cytoreductive nephrectomy and targeted therapy in primary metastatic RCC. This study will collect tissue in more than 400 patients to investigate prognostic and predictive biomarkers synchronously with sequential state of the art imaging sub-studies. This integrated approach will be directed to other key areas in Urological Oncology such as the management of high-risk localized prostate cancer, new approaches to the management of metastatic bladder and prostate cancers and imaging and treatment stratification in testis cancer.
To carry this strategy into the future, and to build on the achievements of the GU Group over the last 35 years, the engagement and contribution of individual clinicians, collaborative cancer trial groups and pharmaceutical companies is of fundamental importance. Considering this we should perhaps reflect on the words contained in Theodore Roosevelt’s 1903 presidential address, in which he said that “the best prize that life offers is the chance to work hard at work worth doing”. The achievements of the last 35 years have undoubtedly been hard earned but they have certainly been worthwhile. It is important that this work continues.

4. Conflict of interest statement

R. Sylvester, L. Collette, N. Clarke, and C.N. Sternberg declare no conflicts of interest. A. Bex is the Principal Investigator of the EORTC 30073 trial which is in part supported by a grant from Pfizer to the EORTC. B. Tombal advised for and received honoraria from Astellas.

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