897 PUBLICATION

Combination therapy with bicalutamide 50 mg plus a luteinising hormone-releasing hormone agonist (LHRHa) is cost effective compared with an LHRHa alone in metastatic prostate cancer

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Background: Combination therapy with bicalutamide ('Casodex') 50 mg plus castration provides an estimated 20% reduction in the risk of death compared with castration alone in patients with metastatic prostate cancer (*BJU Int* 2004; 93: 1177–82). In addition to efficacy, the economic impact of clinical care is an important consideration. We compare here the cost-effectiveness of bicalutamide 50 mg/day plus LHRHa versus LHRHa alone in newly diagnosed men with metastatic (stage D2) prostate cancer.
Materials and methods: The economic model was populated using published data for the following parameters: survival probabilities, specified adverse events; cost; and utility. The key assumption for estimating the incremental cost-effectiveness ratio (ICER) was that patients receiving combination therapy remain on bicalutamide until prostate-specific antigen (ie biochemical) progression occurs and patients remain on LHRHa treatment after progression and until death.
Results: Over 5 years, combination therapy with bicalutamide plus an LHRHa was cost effective both in terms of life-years gained and quality-adjusted life-years (QALYs) gained (see table 1). The cost-effectiveness was even more noticeable at 10 years. These values are well within the acceptable range (<$100,000) for commonly reimbursed medical care interventions.

Table 1: ICER for bicalutamide plus LHRHa vs LHRHa alone

	Per life-year gained	Per QALY gained
5 years	$20,489	$33,677
10 years	$13,313	$20,053

The ICER of bicalutamide plus LHRHa versus LHRHa alone was most influenced by estimates of the survival probabilities for the two interventions. The probability of developing specific adverse events had little impact on the overall conclusions of the model. Importantly, when all the parameters used for the model were varied over a clinically reasonable range, the ICER over 5 years for bicalutamide plus LHRHa versus LHRHa alone remained cost effective (median $27,555 per QALY gained).
Conclusions: Combination therapy with bicalutamide 50 mg plus an LHRHa is a cost-effective option when compared with an LHRHa alone in treating men with metastatic prostate cancer. In light of the recently published findings of survival advantage of bicalutamide plus an LHRHa over LHRHa alone, these findings provide further support for the use of combination therapy with bicalutamide.
'Casodex' is a trademark of the AstraZeneca group of companies

898 PUBLICATION

Bicalutamide combination therapy is cost effective versus flutamide combination therapy in men with metastatic prostate cancer

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Background: Meta-analysis has shown combination hormonal therapy using castration (medical or surgical) plus a non-steroidal antiandrogen provides a significant survival advantage over castration alone in men with metastatic prostate cancer (*Lancet* 2000; 355: 1491–1498). Bicalutamide ('Casodex') and flutamide are the most frequently used non-steroidal antiandrogen components of combination therapy. We estimated the incremental cost-effectiveness ratio (ICER) of bicalutamide versus flutamide, both in combination with a luteinising hormone-releasing hormone agonist (LHRHa).
Materials and methods: An economic model was used to estimate the ICER of bicalutamide 50 mg daily plus LHRHa versus flutamide 250 mg three times daily plus LHRHa in men with metastatic (stage D2) prostate cancer. Published historical data on survival, specific adverse events, costs and utilities were used to populate the model. One- and multi-way analyses were used to assess the sensitivity of the cost-effectiveness estimates.
Results: At 5 years, the ICER for bicalutamide plus LHRHa over flutamide plus LHRHa was $20,000 per life-year gained and $22,000 per quality-adjusted life-year (QALY) gained. At 10 years, the ICER for bicalutamide plus LHRHa over flutamide plus LHRHa per QALY gained was $16,000. These values are favourable and substantially below $50,000–100,000 (the commonly accepted threshold for cost-effectiveness). According to the one-way sensitivity analysis, the cost-effectiveness of bicalutamide plus LHRHa remained favourable across a specified range of values for the predefined tolerability, cost and quality-of-life variables over 5 years (the ICER was most sensitive to differences in patient survival and drug costs). Additionally, a multi-way uncertainty analysis demonstrated that the advantageous ICER remained in the favourable cost-effectiveness range when all the variables in the decision model were varied simultaneously over a clinically reasonable range (median $13,637 per QALY gained over 5 years).
Conclusions: The study results indicate that combination therapy with bicalutamide plus LHRHa is a cost-effective treatment option compared with flutamide plus LHRHa for treating patients with metastatic prostate cancer.
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899 PUBLICATION

A phase II study of sequential chemotherapy with Docetaxel-Estramustine phosphate (DE) followed by Mitoxantrone-Prednisone (MP) in patients (pts.) with metastatic hormone refractory prostate cancer (MHRPC)

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MP and DE are active treatments in MHRPC. These drugs show different mechanisms of action and are not cross-resistent. Because of the low feasibility of concomitant polichemotherapy in MHRPC we have designed the present study with DE followed by sequential MP. Docetaxel 30 mg/sqm weekly plus bid phosphate-estramustine for a total of 12 weeks followed by two weeks rest and mitoxantrone 12 mg/sqm every 3 weeks plus bid 5 mg of prednisone for a maximum of 12 cycles, were administred to MHRPC pts. Primary endpoint was activity (>50% PSA reduction); secondary were: objective responses, toxicities, time to progression, survival and pain control. So far 39 pts have been enrolled. Pts characteristics: median age 71.5 years (55–83), median ECOG PS 1 (range 0–1), median PSA 63.4 ng/ml (7.3–595.5), metastatic sites disease: bone 22, nodes 14, pelvis 5 and liver 2. 354 cycles of Docetaxel (range 3–12) and 161 of Mitoxantrone (range 2–12) have been administred. 35 pts. are evaluable for toxicity and 34 pts for response.
Three episodes of deep venous thrombosis and two congestive heart failures occurred after DE and MP respectively. Except for NCI G3 nail changes in 12% of pts and G3 hepatotoxicity in 16% of pts, G3–4 haematological and non haematological toxicities were observed only in one pt; G1–2 nausea-vomiting occurred in 76% of pts, G1–2 diarrhoea in 76% and G1–2 stomatitis in 64% of pts. Complete PSA response were 12/34 (35%), partial response 13/34 (38%), stable disease 8/34 (23%) and progressive disease 1/25 (2%). According to RECIST criteria 8 pts are evaluable for objective response and 1 RC, 3 RP and 4 SD have been observed. Median time to progression is 7.1 months. DE and MP sequential chemotherapy is feasible and active in MHRPC pts and has a good toxicity profile; accrual is still ongoing.

900 PUBLICATION

Synergistic interaction between ionizing radiation and 8-chloro-adenosine 3', 5'-monophosphate in PC-3 human prostate carcinoma cells

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Background: A novel antineoplastic agent 8-chloroadenosine 3', 5'-monophosphate (8-Cl-cAMP) has been shown to inhibit cell growth and induce cell cycle arrest and apoptosis in a variety of cancers *in vitro* and *in vivo*. It is a new site-selective cAMP analog that down-regulates the regulatory subunit of the cAMP-dependent protein kinase I (PKA-I). The present study explored the cytotoxic and antiproliferative potential of 8-Cl-cAMP and ionizing radiation (IR) in hormone-refractory human prostate cancer cells PC-3.

Material and methods: Prostate cancer cells (PC-3) were treated with either 2–20 Gy of ^{60}Co gamma-IR or 0.5–50 μM 8-Cl-cAMP alone or as an adjuvant immediately after 10 Gy IR. The antiproliferative and cytotoxic effect of these treatments was followed by trypan-blue exclusion assay, MTT assay and BrdU incorporation, while cell cycle distribution and death were analyzed by flow-cytometry of PI stained cells. The combination index value (CI) was calculated by the Calcu syn software.
Results: Both 8-Cl-cAMP and IR showed significant inhibition of PC-3 cell proliferation with IC_{50} of 12.5 μM and 11.9 Gy, respectively, according to BrdU test. The TBE assay showed that the number of viable cells in treated *vs.* control cells (*i.e.* Viability index) decreased, with IC_{50} values of 15 μM and 10.4 Gy, respectively. The Viability index was further decreased when combined treatment was applied, demonstrating synergism (CI 0.5–0.7). Also, CI value for the same combination in BrdU assay demonstrated synergism (CI 0.4–0.9), suggesting that combined treatment significantly enhance either of single treatments of PC-3 cells. Cell cycle analysis showed S and G2/M arrest after all three applied treatments. However, combined tratment also demonstrated significant increase in hypodiploid cell population (18% in treated *vs.* 4% in control cells), suggesting possible induction of apoptosis.
Conclusions: This *in vitro* study indicates that, when used in combination with IR, 8-Cl-cAMP may be effective at concentrations that are lower than those required for efficiency as a single agent. Further preclinical tests should be introduced to confirm if 8-Cl-cAMP in combination with IR could successfully control growth of hormone-refractory prostate-cancer *in vivo*.

901 PUBLICATION

The preferred treatment for stage I seminoma: a survey of Canadian radiation oncologists

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Purpose: To evaluate the preferences for managing stage I seminoma patients post orchiectomy among Canadian radiation oncologists.
Methods: In February 2005 an electronic survey with questions related to the management of stage I seminoma post orchiectomy patients was sent, via email, to Canadian radiation oncologists who treat genitourinary malignancies. The preferences of the respondents with regards to treatment were analyzed and are presented.
Results: Of 119 oncologists surveyed, 93 responded (78% response rate). Fourteen responders did not manage seminoma patients, and one declined to complete the survey. Therefore, the survey completion rate was 74% of the 105 eligible responders. Among the respondents, 89% were male, 11%, female with the median age being 43 years. The median number of years in practice was 13, and 80% worked in academic centres. Responses to questions on the most appropriate and preferred treatment options are presented in table.

Question	Surveillance	Adjuvant radiation	Adjuvant chemotherapy	Unsure
The most appropriate treatment for most stage I seminoma patients	56%	31%	1%	12%
If I had Stage I seminona, I would prefer . . .	52%	27%	8%	13%

There was a strong association between what respondents thought was the best treatment for their patients and what they would choose for themselves ($p < 0.001$). Older oncologists are more likely to choose radiotherapy for themselves ($p = 0.05$) and there is a trend (non-significant) for older oncologist to choose radiotherapy for their patient ($p = 0.07$). Years in practice, type of practice (academic vs. community) and provincial location did not appear to influence management choices.
Conclusions: There remains considerable variation in the opinions of Canadian radiation oncologists regarding the optimal treatment approach for stage I seminoma patients although currently the majority seem to favour surveillance post orchiectomy.

Gynaecological Cancer

Oral presentations (Tue, 1 Nov, 9.15–11.15)
Gynaecological cancer

902 ORAL

Paclitaxel-carboplatin-gemcitabine (TCG) versus paclitaxel-carboplatin (TC) as first line treatment in women with ovarian cancer: A randomized phase III GCIG Intergroup study (AGO-OVAR 9, GINECO-TCG, NSGO-OC-0102)

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Background: Despite major progress achieved in the last decades, epithelial ovarian cancer is still not curable in the majority of patients. Addition of non cross-resistant drugs to standard TC is a potential option for improvement of efficacy. In phase II trials the addition of gemcitabine to TC resulted in high compliance and manageable toxicity. Therefore, a prospectively randomized phase III Intergroup study comparing TCG to standard TC was initiated within the GCIG network.
Patients and methods: This protocol started in 8/02 and recruitment was completed in 04/04. Patients were 18 years or older, had epithelial ovarian cancer FIGO stages IC-IV, and were randomized within 6 weeks after primary surgery. Two-fold stratification was based on centre and disease characteristics: stratum I = FIGO stages IC-IIA, stratum II = FIGO stages IIB-IIC and residual tumor 0–1 cm, and stratum III = FIGO stage IV or residual tumor >1 cm. Patients were randomized to either TC (T 175 mg/m^2 3h iv d1+C AUC 5 iv d1) or TCG (TC as above+G 800 mg/m^2 iv d1+8) for at least 6 cycles every 21 days.
Results: This first interim analysis was based on data from 1,724 patients receiving at least one cycle of study medication, 5.257 cycles of TC and 5,111 cycles of TGC. The strata distribution showed 175, 891, and 676 patients in strata I, II, and III respectively. Most patients received 6+ cycles (87.5% TC, 87.1% TCG). Dose reductions on d1 occurred in <10% in both arms and G d8 was omitted in 37% of cycles. Hematologic toxicity and need for support with G-CSF, blood products and antibiotics occurred significantly more frequent in the TCG arm, but neutropenic fever was rare with 2.1% and 6.5% ($p < 0.0001$). Fatigue was the only non-hematological toxicity showing a significant difference favouring TC (Grade 3/4: 6.6% versus 10.4%, $p = 0.005$). Until 04/05 166 deaths were observed of whom 142 were related to ovarian cancer. The other 24 deaths were equally distributed among patients in both arms and included 5 events possible related to study medication.
Conclusion: TCG was feasible but induced more haematological toxicity. Further follow-up will show if addition of G to TC will provide a meaningful benefit in women with ovarian cancer.
(This study was supported by Eli Lilly & Co).

903 ORAL

Clinical activity of single agent pertuzumab (rhuMab 2C4), a HER dimerization inhibitor, in advanced ovarian cancer (OC): potential predictive relationship with tumor HER2 activation status

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Background: Ovarian cancers (OC) frequently have activation of HER2 even in the absence of HER2 overexpression. Pertuzumab (P), a humanized HER2 antibody, represents a new class of targeted agents called HER dimerization inhibitors (HDIs) that inhibit dimerization of HER2 with EGFR, HER3 and HER4, and inhibit signaling through MAP and PI3 kinases. A phase I trial has demonstrated activity in OC.
Methods: 123 pts. with relapsed OC were treated with P, administered intravenously with a loading of 840 mg followed by 420 mg every 3 weeks to 61 pts. in cohort 1, while 62 pts. in cohort 2 received 1050 mg of P intravenously every 3 weeks. Response rate (RR) by RECIST was the primary endpoint, assessed after cycles 2, 4, 6, 8, 12 and 16. Fresh tumor biopsies were mandatory for cohort 1 in order to assay for HER2 phosphorylation (pHER2) status.