Cervix Cancer Committee
Friday, May 29, 2015, 10:30 a.m. – 12:30 p.m.
LaSalle I Room, Doubletree Hotel, 300 E. Ohio Street, Chicago

Satoru Sagae (JGOG)
Bradley Monk (GOG)
Please sign Attendance Forms

WELCOME & INTRODUCTIONS & COI declarations

Approval of minutes: Nov 2014

Published(1):


Published(2):


In preparation:

1. Surgery plus Radiation +/− CT

post operative radiation
KGOG-0801/GOG263 (RTOG): RT vs CCRT in intermediate risk cervix cancer after hysterectomy
RTOG-0724 (GOG): ChemoRT with and without adjuvant chemotherapy in high risk cervix cancer after hysterectomy

NAC+surgery VS CCRT
EORTC 55994: Randomized phase III study of NAC followed by RH vs CCRT in FIGO stage Ib2, Ia>4 cm or IIb cervical cancer
Casado completed June 2014 total 625 pts

Paraaortic Lymphadenectomy
G-GOC LiLACS Lymphadenectomy in Locally Advanced Cervix Study
Stage IB2–IVA Cervical Cancer PET (+) Pelvic Nodes/ (−) Paraaortic Nodes
Laparoscopic Paraaortic Lymphadenectomy /Tailored ChemoXRT (Experimental) vs Whole Pelvic Chemoradiation Therapy (Standard of Care) Frumovitz 20 −> 24/600
2. Chemoradiation related trials:

KGOG–Thai TACO: (RTOG, GICOM) (CCRN – 61 Viet Nam, Thailand, ? Russia, ?India)
Randomized Clinical Trial of Weekly versus Tri–Weekly Cisplatin based Chemoradiation in Locally Advanced Cervical cancer
Ryu 75→130→168/590

ANZGOG OUTBACK: (120 ANZGOG, 438 NRG oncology ) (CCRN – 0 Columbia, Brazil, ?) :
Chemoradiotherapy +/- adjuvant chemotherapy
Mileshkin 254→432→558/780

NCRI: INTERLACE: (CCRN – 0 GICOM, MaNGO)
Induction ChemoThERapy in Locally Advanced CErvical Cancer.
McCormack 14→38→60/700

RTOG: TIME–C  A RANDOMIZED PHASE III STUDY OF STANDARD VS. IMRT PELVIC RADIATION FOR POST–OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER:
Small 146/284

3. minimal invasive surgery related trials:

NCIC–CTG CX 5 SHAPE: (DGOG, ) (CCRN – 0 ) A RANDOMIZED TRIAL COMPARING RADICAL HYSTERECTOMY AND PELVIC NODE DISSECTION VS SIMPLE HYSTERECTOMY AND PELVIC NODE DISSECTION IN PATIENTS WITH LOW RISK EARLY STAGE CX CA:
Plante 11→50→81/700
G–GOC ConCerv Conservative Surgery for Early Stage Cervical Cancer: Tailoring Radicality to Risk Factors  
CONE+PLN, SH+PLN, cut-through hyst  
Schmeler  
48→ 53 /102 enrolled

G–GOC LACC A Phase III Randomized Clinical Trial of Laparoscopic or Robotic Radical Hysterectomy versus Abdominal Radical Hysterectomy in Patients with Early Stage Cervical Cancer  
Ramirez  
357→ 380/740

GOG–0278 Conservative surgery (cone/nodes or hyst/(nodes) in early stage cervical cancer. (evaluation of physical function and QOL)  
Monk  
9→? –> ?/220

4.Vulvar Cancer
DGOG GROINSS–V II (EORTC, GOG) : Groningen International Study on Sentinel Nodes in Vulvar Cancer  
Creutzberg for van der Zee  
1,037 cases

GOG–0279 Phase II Trial Evaluating Cisplatin (NSC #119875) and Gemcitabine (NSC #613327) Concurrent with Intensity–Modulated Radiation Therapy (IMRT) in Treatment of Locally Adv. SCC of the Vulva  
Monk  
9→? –> ?/52
1. Randomized trials of hypo fractionation – D Gaffney (RTOG)

2. A phase II trial of Neo–adjuvant chemotherapy and fertility sparing surgery for stage IB1 cervix cancer (2–4 cm) – M. Plante (NCIC)

3. International survey of sentinel lymph node biopsy in cervical cancer – J. Sehouli (NOGGO)

4. International prospective validation trial of sentinel node biopsy in cervical cancer – F. Lecuru (GINECO)

5. 1st line metastatic disease adding or versus bevacizumab – K. Tewari (GOG)

6. High risk maintenance trial – T. Herzog (GOG)

7. A randomized phase II study of HPV therapeutic vaccine Transgene TG4001 combined with anti–PD–1 antibody for patients with cervical cancer – S. Scholl (EORTC)

DISCUSSION
Hypofractionated RT in Cervix Cancer

David Gaffney
Definitive CRT: Trial Example

44 Gy/22 fractions

37.5 Gy/15 fractions

7 Gy x 4 Brachy

9 Gy x 2 Brachy

EBRT + SURGERY

ENDPOINT: RFS
Hypofractionation: Where do we go from here?

• Goal: Improve care delivery, not improving OS
  – May need public funding
• Culturally sensitivity and practical
• Integration with chemo: watch out for acute toxicity
• Remember: Our standard need not be the standard elsewhere
  – Some countries have no cervical cancer care
Neo-adjuvant chemotherapy and fertility sparing surgery for stage IB1 cervix cancer (2-4 cm)

Marie Plante (NCIC)
Jeffrey Goh & Vivek Arora (ANZGOG)

GCIG Meeting Chicago – May 2015
NACT + fertility preserving surgery

- Substantial response to NACT
  - CR/OPR: 71%

- Recurrence rate
  - Worrisome in suboptimal responders

- Fertility preservation high: 80%

- Obstetrical outcome: good
Unresolved issues

- Staging lymph node dissection prior to NACT?
- Radical vs simple trachelectomy vs cone post NACT?
- Best chemotherapy regimen?
Outcome measures

• Primary end point
  • Successful fertility preservation defined as intact uterine corpus with no adjuvant XRT

• Secondary end points
  • Response rates to chemotherapy
  • Toxicity
  • Proportion requiring trimodality treatment
  • QoL indices / Ovarian function indices
  • 3 and 5 year disease free survival
International survey about the sentinel lymph node biopsy in cervical cancer

Planed survey of the NOGGO within the GCIG

Jalid Sehouli
Sentinel node biopsy (SLN)

- Cervical cancer < 2 cm
- Sensitivity: 92A%,
- NPV: 98.2% (100% if bilateral).
- Bilateral detection: could spare 75% of complete pelvic dissection (IA1 L1-IIA)
- Bilateral detection: questionable need for parametrial resection (IA2 – IB1)
- Ultrastaging increases identification of nodal metastasis
- Possible ↓ morbidity, including ↓ adhesions.

- Lack of studies
- Unclear strategy (one- vs two-stage approach)
- High false negative rate (µ MTS)
Questionnaire

• Which department are you working in?
• What kind of hospital do you work in?
• How many patients with invasive cervical cancer (CC) have been treated in your hospital in the last 3 years?
• How many patients with CC have been treated in your hospital last year?
Next steps

- Please send remarks within the next 2 weeks to m.keller@charite or jalid.sehouli@charite.de
- Start: 1st of July
- Duration: 6 Month
- Analysis at the next meeting in Chicago 2016
Cervix cancer committee

International prospective validation trial of sentinel node biopsy in cervical cancer

N Abu-Rustum, F Lécuru, P Mathevet, M Plante.

F Bonnetain (Statistics)
G Chatellier (Clinical Research Unit)

For GINECO Group
Sentinel Node Biopsy – early cervical cancer

- Feasibility
- Reproducibility
- Diagnostic accuracy
- Anatomical information
- Histological information (prognosis?)
- Reduced morbidity
- Similar prognosis
- Useful data

*: high NPV in case of bilateral detection

Altgassen G & al 2008
Lécuru F & al 2011
Plante M, Roy M & al 2011
Cormier B & al 2011
Objectives

- Main objective: « co-primary » disease free survival and health related quality of life
  - non-inferiority of SLN biopsy vs SLN biopsy + lymphadenectomy
  - superiority of SLN biopsy
  - The hypothesis is that SLN biopsy alone provides similar survival and better quality of life.

- Secondary objectives:
  - Longitudinal and other dimensions of health related Quality of life.
  - Positive and negative predictive values of SLN biopsy.
  - Outcome of pN1 patients according to the size of metastasis and treatment.
  - Overall survival.
  - Recurrence free survival.
Validation study

- Comparison of prospective cohorts

- Centers with SLN only vs centers with SLN + systematic lymphadenectomy
  - Surgeon qualification, “Cormier algorithm”, pathology, etc.
  - Comparison of SLN negative patients
  - Prospective matching 1:1 according to stage, date Dg, age, tumor diameter
  - Co-primary: DFS & QoL
READY, SET, PINK!

CERVICAL CANCER

FIRST-LINE THERAPY OF RECURRENT/PERSISTENT AND METASTATIC CERVICAL CARCINOMA

Krishnansu S. Tewari, MD, FACOG, FACS
Professor & Director of Research

The Division of Gynecologic Oncology
University of California, Irvine
STRATEGIES

• Addition of other classes of anti-vascular therapy
  – Oral TKI, VDA, TNP-470

• Change chemotherapy backbone
  – Carboplatin-Paclitaxel, others

• Biomarker driven
  – VEGF, synthetic lethality, mTORi, others

• Immuno-Oncology
  – Checkpoint inhibition, autologous T cells, E7-based vaccination

• Stereotactic radiosurgery for oligometastases
PROPOSAL FOR GOG 240R
Biomarker Driven Phase II Trial

**GOG 240 Eligibility Criteria**

- Angiogenesis
- PI3K/Akt/mTOR
- HRD*

*assessed via genomic scar signatures

**Treatment Regimens**

- **CDDP 50 mg/m²**
  - Paclitaxel 135 or 175 mg/m²
  - Bevacizumab 15 mg/kg
  - Plus other VEGF or non-VEGF pathway inhibition

- **CDDP 50 mg/m²**
  - Paclitaxel 135 or 175 mg/m²
  - Bevacizumab 15 mg/kg
  - Plus mTORi

- **CDDP 50 mg/m²**
  - Paclitaxel 135 or 175 mg/m²
  - Bevacizumab 15 mg/kg
  - Plus PARPi

Treat until progression, unacceptable toxicity, or patient voluntary withdrawal.
AIM2CERV:

PHASE III TRIAL OF ADJUVANT ADXS11-011 ADMINISTERED PRIOR TO & FOLLOWING CHEMORADIATION AS PRIMARY TREATMENT FOR HIGH-RISK, LOCALLY ADVANCED CERVICAL CANCER COMPARED TO CHEMORADIATION ALONE

THOMAS J. HERZOG, MD
Vector System

- Utilizes listeria monocytogenes (Lm): gram positive bacteria which selectively infects antigen presenting cells.

- Ideal vector for producing cellular immune response
  - Powerful Innate Immunity
  - Access to APCs (circulating and tissue-based)
  - Secrete Fusion Protein: tLLO-TAA within APC
  - Adaptive Immunity
  - Changes Tumor Microenvironment
  - Vector can be cleared with antibiotics
  - Can be administered repeatedly; no neutralizing antibodies

Technology

- Genetically alters the bacteria to secrete multiple copies of tumor associated antigen fused to highly immunogenic peptide listeriolysin O (LLO)
Advaxis Sponsored Ph 3: ADXS11-001 Administered Following Chemoradiation as Adjuvant Treatment for High Risk Locally Advanced Cervical Cancer: **AIM2CERV**

Cervix Cancer

- FIGO IB2, IIA2 and IIB with + pelvic nodes
- FIGO IIIA, IIIB and IVA
- All FIGO stages with + para-aortic nodes

R 2:1

*N* = 450

**ARM A**
- Placebo
- wks 3, 6, 9 and every 8 wks for 1 year (ie. 8 doses)

**ARM B**
- ADXS-HPV
- wks 3, 6, 9 and every 8 wks for 1 year (ie. 8 doses)

1º endpoint: Progression Free Survival
2º endpoint: Overall Survival

*Concurrent chemo radiation therapy administered with curative intent according to national/institutional guidelines*
Cervical cancer session
Chicago May 29th, 2015

Precision medicine in cervical cancer
A randomized phase II study of HPV therapeutic vaccine Transgene TG4001 combined with anti-PD-1 antibody for patients with cervical cancer
RATIONALE for TG4001 vaccine

• **Over 90% of cervical cancer patients are positive for HPV viral antigen**
  – 60-65% of HPV16.

• **TG4001 vaccine**: MVA modified poxvirus carrying and expressing
  – mutation-inactivated human papilloma virus 16 (HPV16)
  – E6 and E7 oncoproteins

• In phase II and III clinical trials, TG4001 demonstrated **safety and promising clinical response and efficacy** in 50% of women with CIN2/3 lesion caused by HPV16.

• **Cross reactivity in viral types other than HPV16**
  all high risk HPV types according to the Roche linear array diagnostics test can be included in a therapeutic vaccine trial

• HPV genotypes include: 6, 11, **16, 18**, 26, **31, 33, 35, 39**, 40, 42, **45, 51, 52**, 53, 54, 55, 56, **58, 59**, 61, 62, 64, 66, 67, **68**, 69, 70, 71, 72, 73 (MM9), 81, 82 (MM4), 83 (MM7), 84 (MM8), IS39, and CP6108 (**high-risk viral types are in bold**).
Rationale for PD1 or PDL1 blockade

mouse models and clinical trials

• Antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells
  – and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities.

• PD-1 blockade has shown to be useful in many cancers, including cervical cancers and is expected to prolong survival significantly
Combination trial

Expected to significantly increase patient survival

- Vaccine increases pool of reactive T cells
- Checkpoint inhibitor prolongs their lifespan
Thank you so much for your participation and wonderful discussion

See you in TOKYO November 2015
Welcome to 5th OVCCC and GCIG fall meeting

IGCS 2018 in KYOTO