

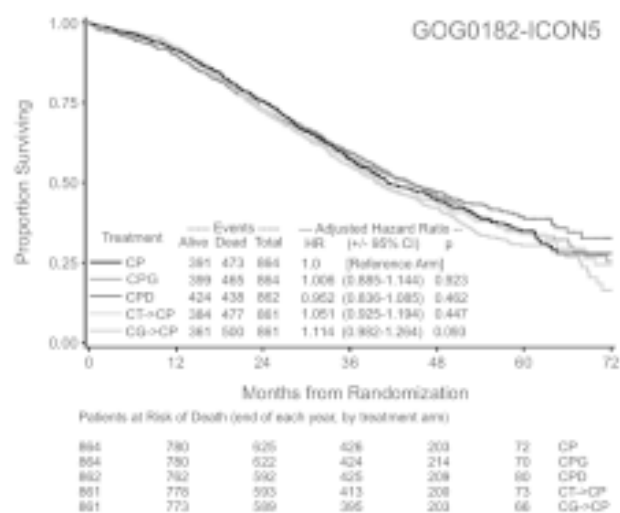
Perspectives in the Management of Ovarian Cancer

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During the last 30 years, more than 20 thousand women from around the globe have participated in randomized trials that have contributed to our understanding of ovarian cancer biology and helped to define optimal treatment strategies. However, prospective randomized trials are not always perfectly designed, or flawlessly executed, and their definitive results only become available several years after activation. As such, emerging data need to be interpreted, and re-interpreted, within an evolving paradigm of biology, disease management, and clinical resources. In addition, not all important questions are feasible to address using prospective randomized trials, and we have traditionally accepted some inferences that emanate from subset analysis, non-randomized trials, historical controls, retrospective data, and consensus panels.

Progress has generally been incremental, and slower than we appreciate. The role of cytoreductive surgery and platinum-based chemotherapy seems clear. In addition, it is generally accepted, but not universally established, that taxanes should be integrated with primary therapy. There continues to be substantial debate regarding the merits of intraperitoneal therapy, in view of excessive non-hematologic toxicity, lack of data with optimal control arms, and the potential impact of weekly taxane administration in the context of published studies with intraperitoneal therapy. In spite of some initial enthusiasm, none of the randomized trials addressing maintenance or consolidation have achieved meaningful improvements in clinical outcomes. Incorporation of a third cytotoxic agent, in spite of compelling preclinical rationale, and interesting clinical data, has not demonstrated any improvement in time to progression or

overall survival when evaluated in several international randomized phase III trials (see figure). Although this particular hypothesis was not validated, a successful collaboration of international cooperative groups developed through the Gynecologic Cancer InterGroup (GCIg), which has helped to share information,



guiding the development of ongoing and future trials.

Attention has appropriately shifted to newer cytotoxic agents, molecular targeted therapeutics, and immunologic strategies. Encouraging data has emerged with inhibition of VEGF, primarily with the use of bevacizumab, and this has prompted several large randomized trials, with the first interim analysis of progression-free survival anticipated in late 2009 (GOG0218). The number and diversity of new agents has challenged our classic clinical trials paradigm, and we need to consider new strategies to efficiently evaluate new agents and combinations. We also need to develop better mechanisms for collaboration among pharmaceutical sponsors, as smaller companies bring innovative ideas forward.

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This presentation will focus on how we have arrived at key management decisions (with or without consensus) related to therapy of ovarian cancer, as well as questions that remain to be resolved. Disease management has been guided not only by phase III trials, but from knowledge

of cancer biology, including trials conducted in the setting of recurrent disease or maintenance. Together, this knowledge has influenced surgical guidelines and choice of primary chemotherapy, both in the setting of clinical trials and standard care.

The table below summarizes many of the key biologic and historical observations that have an impact on the management of ovarian cancer, together with references related to ovarian cancer:

BIOLOGIC OBSERVATIONS		
Type I/II Tumours	Definition of clinical and molecular characteristics to differentiate low-grade and borderline tumours (Type I) from high grade serous tumours (Type II).	Distinct origin of LMP and high-grade tumours has been verified, reinforcing clinical management strategies [1] [2]. Emphasizes need or controlled trials to evaluate treatment options for recurrent low grade tumours.
Early-Stage Disease	Understanding clinical features and risk factors associated with early-stage disease	Recognition of distinct distribution of histologic subtypes in early-stage disease; importance of complete surgical staging: EORTC-ACTION [3] [4]; risk of recurrence associated with high-grade serous histology and/or positive peritoneal cytology; clarification of risk associated with well-staged clear cell tumours; potential for survival impact of adjuvant therapy in high-risk serous tumours: GOG [5]
Advanced-Stage Disease	Analysis of prognostic factors	Verification that mucinous tumours are poorly-responsive to platinum based herapy with inferior long-term clinical outcomes: UK [6], GOG [7], and that age is a negative prognostic factor
Stem Cell Hypothesis	Existence of treatment-resistant regenerative subpopulations within a treatment-sensitive tumour	Recognition of the limitations associated with platinum-based primary therapy and the need to explore alternatives guided by molecular and genomic analysis [8] [9]
Epithelial-Mesenchymal Transition	Characterization of markers associated with transition from epithelial to high-grade invasive mesenchymal phenotype	Molecular basis for carcinosarcoma and high-grade epithelial malignancies, activation (and targeting) of SRC-associated pathways [64]
Synthetic Lethal Paradigms	Genetic and epigenetic silencing of pathways involved in DNA repair	Opportunity to exploit synthetic lethality using PARP inhibition (+/- chemotherapy) in tumours with loss of BRCA function [10] [11]; epigenetic silencing of BRCA [12] [13]; recognition of secondary mutations in BRCA associated with platinum resistance [14] [15]
SURGICAL INTERVENTIONS		
	Extent of cytoreductive surgery	Extent of post-operative residual disease clearly correlates with outcome [16], but the requirement for cytoreductive surgery has not been validated in a randomized trial. Multiple retrospective studies confirm that women who undergo "maximum" cytoreductive surgery will have improved median survival [17] [18], but the degree of surgical effort has not been validated in a prospective randomized trial. As such, the relative impact of tumour biology vssurgical skill remains unresolved.
Surgical Interventions	Timing of cytoreductive surgery	Interval cytoreduction is superior to no cytoreduction: EORTC [19]; initial cytoreduction followed by interval cytoreduction in appropriate patients is equivalent to initial cytoreduction alone: GOG0152 [20] [21]. For patients with advanced IIIC-IV disease, neoadjuvant chemotherapy with interval cytoreduction achieves equivalent survival to initial cytoreduction, with improved safety (EORTC-NCIC Phase III) [IGCS]
	Role of secondary surgical assessment	Secondary surgical assessment for patients in clinical complete remission will provide prognostic information, but surgery has not been shown to have an impact on survival or optimization of secondary treatment: GOG0158 [22]

CHEMOTHERAPY AND MOLECULAR TARGETED INTERVENTIONS		
Platinum Agents	Cisplatin <i>vs</i> Carboplatin	Carboplatin associated with equivalent long-term outcomes, reduced non-hematologic toxicity, increased hematologic toxicity: SWOG [23], GOG [24], AGO [25].
	Platinum dose intensity	No evidence of improved long-term outcomes within ranges achieved using conventional therapy or hematopoietic progenitor cell support: DCOG [26], LGOG [27]
	Dose intensity and infusion duration	Infusion duration correlates closely with hematologic toxicity, but not efficacy. No evidence for dose-response relationship within usual clinical dose ranges: NCIC-EORTC [28], GOG [29] [30] [31]
	Incorporation in primary therapy	Improved median survival with incorporation of paclitaxel: GOG111 [32], OV10 [33] [34].
	Weekly therapy	Improved therapeutic ratio (phase I-II): MSKCC [35], GOG [36] and improved progression-free survival (phase III): JGOG [37] associated with weekly therapy .
Taxanes	Alternative agents	Docetaxel associated with different toxicity profile, but without improved long-term outcomes: SCOTROC [38]. Epothilones have similar activity with different toxicity profiles. Tubulin α -III isoform emerging as predictors of resistance [65] [66] [67].
	Intraperitoneal cisplatin	Improved survival validated in phase III trials, but with increased toxicity GOG0104 [39], GOG0114 [40], GOG0172 [41], Meta-analysis [42] [43], Commentary [44] [45]
	Intraperitoneal carboplatin	Reduction in toxicity, but activated more slowly, compared to cisplatin. Awaiting randomized trials for validation
Intraperitoneal Therapy	Intraperitoneal paclitaxel	Incorporated in phase III program, but importance unclear [41]
Incorporation of Additional Cytotoxic Agents	Gemcitabine, epirubicin, PEG-liposomal doxorubicin, topotecan	Extensively evaluated through international phase III trials involving multiple GCI members. No evidence for improved progression-free or overall survival with any new regimen: AGO-GINECO (epirubicin) [46], NSGO (epirubicin) [47], AGO (gemcitabine) [IGCS], NCICEORTC (topotecan) [48], MITO (topotecan) [49], GOG0182 (multiple) [50]
Targeted Cytotoxic Agents	Antifolates, trabectedin and other xenobiotics, Aurora Kinase A inhibition, Kinesin Spindle Protein inhibition	Activity of trabectedin in platinum-sensitive recurrent disease [77]. Limited activity in platinum-resistant disease (except for pemetrexed) [78] [79]
	VEGF, VEGFR, angiopoietin-2, HIF1 α , VEGFR-TKI	Positive phase II data with Bevacizumab anti-VEGF antibody: GOG[51], Industry Phase II [52], followed by phase III front-line trials (GOG0218, OV7) in combination
		Limited activity with Aflibercept VEGF-trap single agent
		Activity with VEGFR-TKI Phase II: Pazopanib [80] and Cediranib [81], followed by phase III trials in small-volume disease (in progress)
		Potential increased response rate with combinations of anti-VEGF and VEGFR-TKI (sorafenib), but with increased toxicity [76]. Most combinations unexplored

Molecular Targeted Agents	EGFR, HER2/neu, HER3	Cetuximab (anti-EGFR) single-agent and in combination with chemotherapy [68], limited activity. Herceptin (anti-HER2) single-agent in HER2-positive tumours, limited activity [69]. Pertuzumab (anti-HER2) single agent, limited activity [70], relationship to HER3 expression [71]. Gefitinib (EGFR TKI) single agent [72], activity limited to receptor mutations [73]. Erlotinib limited activity [74]. Lapatinib (dual TKI) single agent, limited activity.
	IGFR1, FGF, HGF, Integrins	Antibody-based strategies under evaluation
	MAPK, MEK, ERK, SRC	(TKI) TKI-based strategies under evaluation
	TRAIL, IAP	Early studies in progress
	Notch, Hedgehog	Early studies in progress
MAINTENANCE OR CONSOLIDATION		
Maintenance with Cytotoxic Agents	Evaluated with topotecan, epirubicin,	paclitaxel, IP platinum. No improvement in survival from completed trials: Epirubicin [53] Topotecan [54] [55], Paclitaxel [56], IP Platinum [57]. Trial in progress with paclitaxel and polyglutamated paclitaxel (GOG0212)
Maintenance with Biologic Agents	Evaluated with interferon-alpha, 90Y-anti-HMFG1 antibody, murine anti-CA125	No improvement in survival from completed trials: 90Y-anti-HMFG1 [58], Oregovomab [59], Interferon- α [60]. Trials in progress with other antibodies, bevacizumab, and VEGFR-TKI.
REGULATION OF THE IMMUNE RESPONSE		
Immunologic Factors and Interventions	Cytokines	Interferon- α -1b: Phase III evaluation in combination with chemotherapy, no improvement in survival [61]
	Antibody-Based Interventions	Oregovomab (murine anti-CA125): Phase III maintenance, no improvement in survival, but identification of favorable subpopulation based on generation of an immune response, suggesting that regulation of the immune response could have an impact in the setting of established disease [59]. Abagovomab (murine anti-idiotypic CA125) studies in progress [75].
	Intratumoural T lymphocytes	Improved survival associated with higher number of tumour infiltrating lymphocytes [62] and lower ratios of immunoregulatory T lymphocytes [63]
	Vaccines	Autologous, peptide-based, and dendritic cell strategies under evaluation
	Co-Regulatory Molecules	Anti-CTLA4 studies in progress

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