The Need for Level 1 Clinical Evidence in Daily Practice

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8.1 What Is Evidence-Based Medicine?

It is difficult to begin to describe evidence-based medicine (EBM) without first mentioning Dr. David Sackett. A Chicago-born and bred internal medical physician who quickly switched his career path to clinical epidemiology, Dr. Sackett went on to make enormous contributions to clinical community. By placing importance on the understanding and measurement of patient adherence to prescribed treatments, the methodology of randomized control trials (RCTs), Dr. Sackett's influence has led to the improvements in patient care across indications beyond his own specialty field [1]. Fundamentally, his work led to a mind-set shift in the way clinicians and academic authorities thought about the role of evidence in clinical care. In doing so, he laid the foundation for EBM, which is defined as the process of systematically reviewing, appraising, and using clinical research findings to aid the delivery of optimum clinical care to patients [1]. Dr. Sackett himself describes this practice as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients [2]. Since its early definitions in clinical epidemiology, the concept of EBM has been recognized by hundreds of thousands of clinicians across the globe and across various medical disciplines [3]. In light of the importance of grading clinical evidence in everyday practice and care, this chapter highlights EBM in the context of endometrial cancer. This chapter describes how good gyne-oncologists use both clinical expertise and the best available external evidence to guide treatment choices for their patients with endometrial cancer.

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M. R. Mirza (ed.), *Management of Endometrial Cancer*,
https://doi.org/10.1007/978-3-319-64513-1_8

8.2 Defining Level 1 Evidence

Evidence-based care requires critical review of published resources for evidence to help direct and guide care for the specific clinical question. These resources are commonly obtained from searches in databases such as PubMed, EBSCO, Cochrane Consumer Network (CCN), field-specific association resources, government sites, and other electric resources. The clinician or practitioner must be able to systematically evaluate the evidence obtained for its relevance and validity as related to the specific clinical question.

There are a number of different hierarchies of evidence available which can be used to rank the strength and validity of the evidence from expert opinion to systematic reviews and meta-analyses (see Tables 8.1 and 8.2, Fig. 8.1). Efficacy is defined as the capacity or power to produce a clinical effect. This can be assessed based on meta-analyses and systematic reviews (Level 1 according to CCN). Evidence guidelines, randomized clinical trials, observational studies, cohort, case control, case series, and case reports address effectiveness—the quality or amount of the effect in practice, outside the laboratory or other controlled environment (Level 2 evidence). Evidence from expert committees, opinions, or clinical experience is considered the lowest grade of evidence due to the higher probability for bias (Level 3).

The clinician or practitioner can incorporate the published evidence, the individual patient's case and their own clinical expertise to develop an appropriate plan of care. Additionally, clinical guidelines or algorithms may be available to assist in care planning. These guidelines are generally developed by a multidisciplinary team with support from professional organizations, institutions, or governmental agencies that publish the guidelines (i.e. ESMO, ASCO, NIH/NCI, EMA etc.).

Table 8.1 Example of grading of evidence

Level	Type of Evidence
I	Evidence is obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power).
II	Evidence is obtained from at least one well-designed experimental study, Randomized trials with high false-positive and/or negative errors (low power).
III	Evidence is obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single-group, pre-post, cohort, time, or matched case-control series.
IV	Evidence is obtained from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies.
V	Evidence from case reports and clinical examples.

Table 8.2 Grades of evidence as per the Oxford Centre for Evidence-Based Medicine (OCEBM)

Level	Type of evidence
1a	Systematic review with homogeneity of randomized control trials
1b	Individual randomized control trial with a narrow confidence interval
1c	All or none related outcome
2a	Systematic review with homogeneity of cohort studies
2b	Individual cohort study (including low-quality randomized control trials, e.g., <80% follow-up)
2c	"Outcomes" Research; Ecological studies
3a	Systematic review with homogeneity of case-control studies
3b	Individual case–control study
4	Case-series (and poor-quality cohort and case–control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
Grades of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

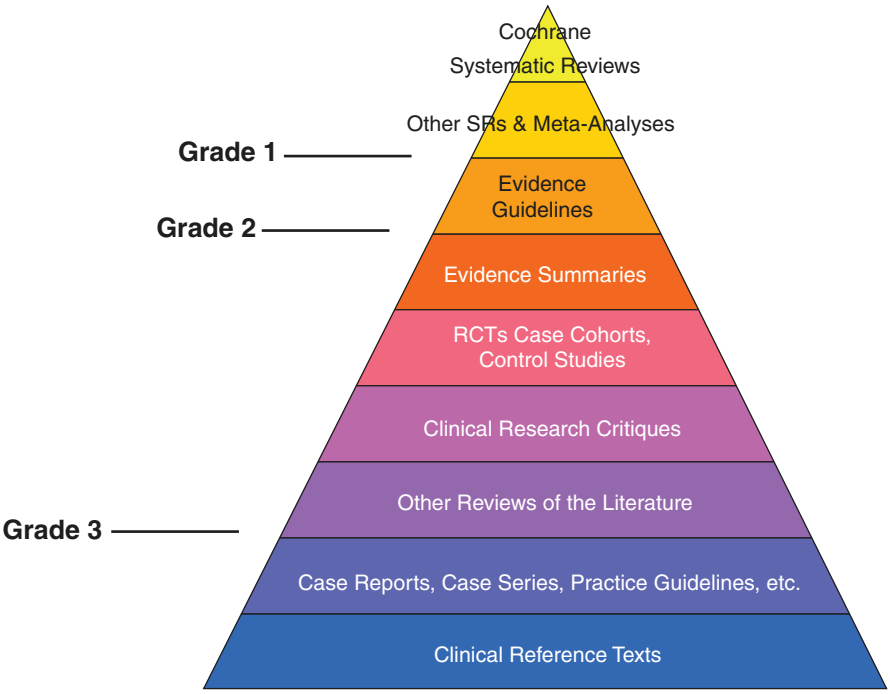

Fig. 8.1 Grades of evidence as per the Cochrane Consumer Network (CCN)

8.3 Why Are Randomized Clinical Trials Needed?

The National Cancer Institute classifies RCTs as a study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. RCTs have been ubiquitous in Phase III settings over the past half century [4]. RCTs serve as the basic clinical research tool for evaluating new interventions or existing methods previously not tested [4]. The methodology for the design, conduct and analysis of clinical trials has evolved greatly but the need has not changed. RCTs today still stand as the most effective way to discriminate the effects of treatments for a given patient population.

Given the variation in clinical trial design, not all RCTs can be defined as equal in terms of their objectivity. Chalmers et al. [5] were among the first to suggest the importance of evaluating the design, implementation, and analysis of RCT. The qualification of RCTs was suggested to be based on four factors: (1) basic descriptive material, (2) the study protocol, (3) the analysis of the data, and (4) data useful for potential combining of several RCT results [5]. By considering these factors in clinical evidence, a clinician is equipped with tools to determine whether new findings in an indication should be considered in the treatment plan of patient population. Table 8.3 offers an overview of intervention RCTs currently conducted in endometrial cancer, which are either complete, actively recruiting or not yet recruiting (search conducted on www.clinicaltrials.gov, accessed 9th October 2017). The outcomes of these studies will guide the future standard of care options for patients with endometrial cancer.

8.4 Primary End-Points in Clinical Trials Matter

There is no single ideal clinical trial end-point for all situations, but there are many new ways to define end-points beyond the classical terms. Given that most cases of endometrial cancer are diagnosed in women who are past menopause and aged in their mid-60s, the primary endpoints which are selected in new RCTs should be carefully matched to the needs of this patient population. In the European context, there has been recent scrutiny over the lack of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency (EMA) since 2009 by a retrospective cohort study [6]. This suggests that more than ever before must clinicians carefully design their trials to incorporate the most favorable outcomes for patients especially in intervention studies. Below is a list of classical primary end-points used as well as some new options that are becoming increasingly more popular in new clinical trial designs.

Overall Survival (OS)—high impact for patients but its relevance can be hampered in elderly patients due to death by other causes and does not include QoL.

Table 8.3 Currently active or complete RCTs in endometrial cancer

Status	Study title	Intervention
Completed	2D Versus 3D Radical Laparoscopic Hysterectomy for Endometrial Cancer: a Prospective Randomized Trial	Procedure: 3D laparoscopy Procedure: standard laparoscopy
Active, not recruiting	Randomized Trial of Radiation Therapy With or Without Chemotherapy for Endometrial Cancer	Radiation: radiation therapy Drug: cisplatin Drug: carboplatin Drug: paclitaxel
Completed	Zoptarelin Doxorubicin (AEZS 108) as Second Line Therapy for Endometrial Cancer	Drug: AEZS-108/zoptarelin doxorubicin Drug: doxorubicin
Completed	Doxorubicin and Cisplatin With or Without Paclitaxel in Treating Patients With Locally Advanced, Metastatic, and/or Relapsed Endometrial Cancer	Drug: cisplatin Drug: doxorubicin hydrochloride Drug: paclitaxel
Completed	Comparison of Two Combination Chemotherapy Regimens Plus Radiation Therapy in Treating Patients With Stage III or Stage IV Endometrial Cancer	Drug: doxorubicin hydrochloride Drug: cisplatin Biological: filgrastim Biological: pegfilgrastim Drug: paclitaxel
Recruiting	Trial of Letrozole + Palbociclib/Placebo in Metastatic Endometrial Cancer	• Drug: palbociclib/placebo • Drug: letrozole
Completed	Combination Chemotherapy With or Without G-CSF in Treating Patients With Stage III, Stage IV, or Recurrent Endometrial Cancer	Biological: filgrastim Drug: cisplatin Drug: doxorubicin hydrochloride Drug: paclitaxel
Recruiting	Trial Between Two Follow up Regimens With Different Test Intensity in Endometrial Cancer Treated Patients	Procedure: intensive/low-risk follow up (IA G1; IA G2) Procedure: intensive/high-risk follow up (≥IA G3) Procedure: minimalist/low-risk follow up (IA G1; IA G2) Procedure: minimalist/high-risk follow up (≥IA G3)
Completed	Radiation Therapy With or Without Chemotherapy in Treating Patients With High-Risk Endometrial Cancer	Drug: cisplatin Drug: doxorubicin hydrochloride Drug: epirubicin hydrochloride Procedure: adjuvant therapy Procedure: conventional surgery Radiation: radiation therapy
Recruiting	Carboplatin-Paclitaxel ± Bevacizumab in Advanced (Stage III–IV) or Recurrent Endometrial Cancer	Drug: bevacizumab Drug: carboplatin AUC 5 + paclitaxel 175 mg/mq q 21 for 6–8 cycles
Completed	Radiation Therapy or Observation Only in Treating Patients With Endometrial Cancer Who Have Undergone Surgery	Radiation: radiation therapy

(continued)

Table 8.3 (continued)

Status	Study title	Intervention
Recruiting	Hormone Receptor Positive endometrIal Carcinoma Treated by Dual mTORC1/ mTORC2 Inhibitor and Anastrozole (VICTORIA)	Drug: AZD2014 Drug: anastrozole
Active, not recruiting	Doxorubicin Hydrochloride, Cisplatin, and Paclitaxel or Carboplatin and Paclitaxel in Treating Patients With Stage III–IV or Recurrent Endometrial Cancer	Drug: carboplatin Drug: cisplatin Drug: doxorubicin Hydrochloride Biological: filgrastim Other: laboratory biomarker analysis Drug: paclitaxel Biological: pegfilgrastim
Recruiting	Paclitaxel and Carboplatin With or Without Metformin Hydrochloride in Treating Patients With Stage III, IV, or Recurrent Endometrial Cancer	Drug: carboplatin Other: laboratory biomarker analysis Drug: metformin hydrochloride Drug: paclitaxel Other: placebo
Recruiting	Feasibility Study of Laparoendoscopic Single Site Surgical Staging for Endometrial Cancer	• Procedure: single-port laparoscopic surgical staging • Procedure: four-port laparoscopic surgical staging
Recruiting	Robot Assisted Laparoscopic Hysterectomy vs. Abdominal Hysterectomy in Endometrial Cancer	• Procedure: abdominal total hysterectomy • Procedure: robot assisted laparoscopic hysterectomy
Completed	Temsirolimus With or Without Megestrol Acetate and Tamoxifen Citrate in Treating Patients With Advanced, Persistent, or Recurrent Endometrial Cancer	• Other: laboratory biomarker analysis • Drug: megestrol acetate • Drug: tamoxifen citrate • Drug: temsirolimus
Active, not recruiting	Carboplatin and Paclitaxel With or Without Cisplatin and Radiation Therapy in Treating Patients With Stage I, Stage II, Stage III, or Stage IVA Endometrial Cancer	Drug: carboplatin Drug: cisplatin Radiation: internal radiation therapy Drug: paclitaxel Other: quality-of-life assessment Radiation: radiation therapy
Active, not recruiting	Trametinib With or Without GSK2141795 in Treating Patients With Recurrent or Persistent Endometrial Cancer	• Drug: Akt inhibitor GSK2141795 • Other: laboratory biomarker analysis • Drug: trametinib
Completed Has results	The Study of Oral Steroid Sulphatase Inhibitor BN83495 Versus Megestrol Acetate (MA) in Women With Advanced or Recurrent Endometrial Cancer	• Drug: BN83495 • Drug: megestrol acetate (MA)

Table 8.3 (continued)

Status	Study title	Intervention
Completed	Clinical Trial of Ridaforolimus Compared to Progestin or Chemotherapy for Advanced Endometrial Carcinoma (MK-8669-007 AM6)	• Drug: ridaforolimus • Drug: medroxyprogesterone acetate tablets • OR megestrol acetate • Drug: chemotherapy
Active, not recruiting	Laparoscopic Approach to Cancer of the Endometrium	• Procedure: total abdominal hysterectomy • Procedure: total laparoscopic hysterectomy
Recruiting	Combination Chemotherapy With Nintedanib/Placebo in Endometrial Cancer	Drug: nintedanib or placebo; carboplatin, paclitaxel
Active, not recruiting	Everolimus and Letrozole or Hormonal Therapy to Treat Endometrial Cancer	• Drug: everolimus • Drug: tamoxifen • Drug: letrozole • Drug: medroxyprogesterone acetate
Completed	Tachosil for the Prevention of Symptomatic Lymph Cysts	Drug: tachosil fibrin patch
Recruiting	Evaluation of Sentinel Node Policy in Early Stage Endometrial Carcinomas at Intermediate and High Risk of Recurrence	Drug: pre-operative SN mapping with nanocis Drug: intra-operative SN mapping with patent V blue dye Drug: Intra-operative SN mapping with indocyanin green Procedure: full bilateral laparoscopic lymphadenectomy and hysterectomy Procedure: current initial staging protocols
Completed	Laparoscopic Surgery or Standard Surgery in Treating Patients With Endometrial Cancer or Cancer of the Uterus	• Procedure: laparoscopic surgery • Other: quality-of-life assessment • Procedure: therapeutic conventional surgery
Completed	Radiation Therapy or No Further Treatment Following Surgery in Treating Patients With Cancer of the Uterus	• Radiation: radiation therapy
Completed	A Study Assessing the Safety and Utility of PINPOINT® Near Infrared Fluorescence Imaging in the Identification of Lymph Nodes in Patients With Uterine and Cervical Malignancies Who Are Undergoing Lymph Node Mapping	• Device: PINPOINT
Recruiting	The Efficacy and Safety of the Postoperative Adjuvant Treatment in Patients With High-risk Stage I Endometrial Carcinoma	Drug: paclitaxel Drug: paraplatin (carboplatin injection) Radiation: pelvic radiation Radiation: vaginal brachytherapy 1 Radiation: vaginal brachytherapy 2

(continued)

Table 8.3 (continued)

Status	Study title	Intervention
Completed	Hormone Therapy in Preventing Endometrial Cancer in Patients With a Genetic Risk For Hereditary Nonpolyposis Colon Cancer	• Drug: medroxyprogesterone • Drug: ethinyl estradiol • Drug: norgestrel • Other: laboratory biomarker analysis
Completed	Lifestyle Change and Quality of Life in Obese Patients With Stage I/II Endometrial Cancer in Remission	• Behavioral: behavioral dietary intervention • Other: counseling intervention • Other: educational intervention
Completed	Exercise and Healthy Diet or Standard Care in Patients in Remission From Stage I or Stage II Endometrial Cancer	• Behavioral: behavioral dietary intervention • Behavioral: exercise intervention • Other: counseling intervention
Active, not recruiting	Robotic Versus Abdominal Surgery for Endometrial Cancer	• Procedure: robotic surgery • Procedure: abdominal surgery
Recruiting NEW	A Study of Ketogenic Diet in Newly Diagnosed Overweight or Obese Endometrial Cancer Patients	• Other: ketogenic diet (KD) • Other: standard diet (SD)
Recruiting	Assisted Exercise in Obese Endometrial Cancer Patients	• Behavioral: exercise on stationary recumbent exercise cycle • Behavioral: health education • Behavioral: questionnaires
Active, not recruiting	Evaluation of Carboplatin/Paclitaxel With and Without Trastuzumab (Herceptin) in Uterine Serous Cancer	• Drug: carboplatin/paclitaxel • Drug: trastuzumab
Completed	Surgery With or Without Lymphadenectomy and Radiation Therapy in Treating Patients With Endometrial Cancer	• Procedure: adjuvant therapy • Procedure: conventional surgery • Radiation: brachytherapy • Radiation: radiation therapy
Completed	Comparison of Radiation Therapy With or Without Combination Chemotherapy Following Surgery in Treating Patients With Stage I or Stage II Endometrial Cancer	• Drug: cisplatin • Drug: paclitaxel • Procedure: adjuvant therapy • Radiation: radiation therapy
Recruiting	Chemotherapy or Observation in Stage I–II Intermediate or High Risk Endometrial Cancer	• Drug: carboplatin and paclitaxel • Other: observation
Completed	External-Beam Radiation Therapy Compared With Vaginal Brachytherapy After Surgery for Stage I Endometrial Cancer	• Radiation: external beam radiation therapy • Radiation: vaginal brachytherapy
Recruiting	Phase 2 Study of MLN0128, Combination of MLN0128 With MLN1117, Paclitaxel and Combination of MLN0128 With Paclitaxel in Women With Endometrial Cancer	• Drug: paclitaxel • Drug: MLN0128 • Drug: MLN1117

Table 8.3 (continued)

Status	Study title	Intervention
Recruiting	Radiation Therapy With or Without Cisplatin in Treating Patients With Recurrent Endometrial Cancer	• Radiation: 3-dimensional conformal radiation therapy • Drug: cisplatin • Radiation: intensity-modulated radiation therapy • Radiation: internal radiation therapy
Recruiting	Medroxyprogesterone Acetate With or Without Entinostat Before Surgery in Treating Patients With Endometrioid Endometrial Cancer	• Drug: entinostat • Procedure: hysterectomy • Other: laboratory biomarker analysis • Drug: medroxyprogesterone acetate
Completed	Radiation Therapy Compared With Combination Chemotherapy in Treating Patients With Advanced Endometrial Cancer	• Drug: cisplatin • Drug: doxorubicin hydrochloride • Radiation: low-LET photon therapy
Active, not recruiting	Pelvic Radiation Therapy or Vaginal Implant Radiation Therapy, Paclitaxel, and Carboplatin in Treating Patients With High-Risk Stage I or Stage II Endometrial Cancer	• Radiation: 3-dimensional conformal radiation therapy • Drug: carboplatin • Radiation: intensity-modulated radiation therapy
Active, not recruiting	Standard Versus Intensity-Modulated Pelvic Radiation Therapy in Treating Patients With Endometrial or Cervical Cancer	• Radiation: 3-dimensional conformal radiation therapy • Radiation: intensity-modulated radiation therapy
Completed	Olaparib in Combination With Carboplatin for Refractory or Recurrent Womens Cancers	• Drug: carboplatin • Drug: olaparib
Recruiting	Trial of Cisplatin Plus Radiation Followed by Carbo and Taxol vs. Sandwich Therapy of Carbo and Taxol Followed Radiation Then Further Carbo and Taxol	• Drug: cisplatin • Drug: carboplatin • Drug: paclitaxel • Radiation: radiation therapy
Completed	Surgery With or Without Chemotherapy in Treating Patients With Soft Tissue Sarcoma	Biological: filgrastim Drug: doxorubicin hydrochloride Drug: ifosfamide Drug: isolated perfusion Procedure: adjuvant therapy Procedure: conventional surgery Radiation: radiation therapy
Completed	Endometrial Cancer—LOHP Alone and With 5FU	• Drug: oxaliplatin, 5 FU
Recruiting	Selective Targeting of Adjuvant Therapy for Endometrial Cancer (STATEC)	• Procedure: abdominal surgery • Procedure: lymphadenectomy
Completed Has results	Intravenous Weekly Topotecan In Subjects With Recurrent Or Persistent Endometrial Cancer	• Drug: topotecan

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Table 8.3 (continued)

Status	Study title	Intervention
Completed	Systematic Pelvic Lymphadenectomy Versus no Lymphadenectomy in Clinical Stage I–II Endometrial Cancer	• Procedure: systematic pelvic lymphadenectomy
Completed	END-1: First Line Chemotherapy for Advanced or Recurrent Endometrial Carcinoma With Carboplatin and Liposomal Doxorubicin	• Drug: liposomal doxorubicin • Drug: carboplatin
Recruiting	Prospective Randomised Phase II Trial Evaluating Adjuvant Pelvic Radiotherapy Using Either IMRT or 3-Dimensional Planning for Endometrial Cancer. ICORG 09-06	Radiation: 45 Gy/25 fractions
Recruiting	A Study of Durvalumab With or Without Tremelimumab in Endometrial Cancer	Drug: durvalumab Drug: tremelimumab
Recruiting	STELLA 2 Trial: Transperitoneal vs. Extraperitoneal Approach for Laparoscopic Staging of Endometrial/Ovarian Cancer	Procedure: extraperitoneal laparoscopic aortic lymphadenectomy Procedure: transperitoneal Laparoscopic aortic lymphadenectomy
Completed	Targeted Disruption to Cancer Metabolism and Growth Through Dietary Macronutrient Modification	Other: ketogenic diet Other: AND diet
Recruiting	Improving the Treatment for Women With Early Stage Cancer of the Uterus	Drug: levonorgestrel Drug: metformin

Disease-specific survival (DSS)—perhaps a better measure but essentially it does not matter to the patient what the cause of death is.

Progression-Free Survival (PFS)—"the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse".

Functional Decline (FD)—a new endpoint which considers if there are new loss of independence in self-care capabilities associated with deterioration in mobility and in the performance of activities of daily living such as dressing, toileting, and bathing. This end-point can be incorporated into elderly patient trials [7].

Overall Treatment Utility (OTU)—at set intervals: was the treatment worthwhile for the patient? Decided by the patient and the clinician.

Good OTU score: satisfied patient, clinician and low toxicity.

Classical endpoints are frequently not suitable for elderly patient populations. Thus, co-primary endpoints are recommended and statisticians often prefer a composite endpoint which can take into account multiple dimensions. A hallmark example of a composite endpoint (overall treatment utility) is illustrated by FOCUS2, a UK phase II randomized trial in which older and frail patients with inoperable colorectal cancer were randomized to receive treatment with infusional fluorouracil/levofolinic acid or capecitabine or either fluoropyrimiide schedule with the addition

of oxaliplatin [8]. These drugs were administered at 80% of the standard doses. The composite endpoint included measures of response, toxicity, as well as clinician and patient perception of treatment efficacy. This trial is an exceptional example of how clinical trials can address the needs of the patient population at hand with well-designed and rational clinical end-points.

8.5 Clinical Trials in the New Era of Personalized Medicine

Several terms, including *precision medicine*, *stratified medicine*, *targeted medicine*, and *pharmacogenomics*, are sometimes used interchangeably to describe *personalized medicine* [9]. The European Union describes personalized medicine as "providing the right treatment to the right patient, at the right dose at the right time." The National Cancer Institute extends upon this definition by stating that personalized medicine is "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease" [9]. In order to fulfill this health delivery ethos, future clinical trial designs must be able to accessibly integrate molecular analysis such as next-generation sequencing in order to profile patient prior to entry into intervention studies. Furthermore, a number of parallel translational research activities must be performed in order to tailor personalized medicine for future patient populations. Endometrial cancer is no exception to the diseases which can be approached with this transformative healthcare approach. Below are some key definitions of relevant clinical trial designs.

Comparative Trials: also known as controlled, clinical trials involve one group of patients who receive the new drug and a control group who receives a placebo or gold standard treatment. Comparative studies are typically conducted as double-blind trials, where neither the physician nor the patient knows which group is receiving the new drug. Double-blind trials help to eliminate any biased results [10].

Open Label Trials: do not attempt to disguise the new drug or treatment, meaning that no standard treatment or placebo is utilized. This leans towards bias, as both the patient and the physician are aware of which groups are receiving what type of treatment [10].

Basket Trials: test the effect of one drug on a single mutation in a variety of tumor types, at the same time. These studies also have the potential to greatly increase the number of patients who are eligible to receive certain drugs relative to other trial designs [11].

Umbrella Trials: have many different treatment arms within one trial and one indication. People are assigned to a particular treatment arm of the trial based on their type of cancer and the specific molecular makeup of their cancer [11].

The phases of clinical trials are described as I, II, and III below [11].

Phase I Clinical Trials: An experimental drug or treatment, which has proven to be safe for use in animals, is tested in a small group of people (15–30) for the first time. Data are collected on the dose, timing, and safety of the treatment. The purpose is to evaluate its safety and identify side effects.

Phase II Clinical Trial: An experimental drug or treatment is tested in a larger group (100 or less) to provide more detailed information about the safety of the treatment, in addition to evaluating how well it works for a broader range of people. Phase II trials usually take about 2 years to complete.

Phase III Clinical Trials: Before an experimental drug or treatment is approved by the FDA and made available to the public, Phase III trials are conducted on a large group of people (from 100 to several thousand). At least two (and often more than two treatment options, including standard of care) are compared to find out whether the new treatment is better, and possibly has fewer side effects, than the current standard treatment. Phase III clinical trials are usually randomized, meaning that patients receive either the investigational drug or treatment or another drug or treatment in a non-ordered way.

Phase IV Clinical Trial: After a drug is approved by the FDA and made available to the public, researchers track its safety, seeking more information about a drug or treatment's risks, benefits, and optimal use. Several hundred to several thousand people participate in Phase IV trials.

Future clinical trial design for endometrial cancer patients must progress with the innovations achieved across other cancer forms such as the inclusion of a translational research aspects across all phases of trials, pre-stratification of patients via next-generation sequencing (NGS), and or immuno-profiling. Evidence-based medicine is an approach to clinical problem-solving which will continue to drive better treatment options for patients with endometrial cancer.

References

1. Guyatt G. Dave Sackett and the ethos of the EBM community. J Clin Epidemiol. 2016;73:75.
2. Sackett DL, Rosenberg WM, Gray JM, Haynes RB, Richardson WS. Evidence based medicine. Br Med J. 1996;313(7050):170.
3. Fletcher RH, Fletcher SW. David Sackett was one of a kind. J Clin Epidemiol. 2016;73:67–72.
4. DeMets DL. Methods for combining randomized clinical trials: strengths and limitations. Stat Med. 1987;6(3):341–8.
5. Chalmers TC, Smith H, Blackburn B, Silverman B, Schroeder B, Reitman D, Ambroz A. A method for assessing the quality of a randomized control trial. Control Clin Trials. 1981;2(1):31–49.
6. Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. Br Med J. 2017;359:j4530.
7. McVey LJ, Becker PM, Saltz CC, Feussner JR, Cohen HJ. Effect of a geriatric consultation team on functional status of elderly hospitalized patients: a randomized, controlled clinical trial. Ann Intern Med. 1989;110:79–84.
8. Ring A, Harari D, Kalsi T, Mansi J, Selby P, editors. Problem solving in older cancer patients: a case-study based reference and learning resource. Oxford: Clinical Publishing; 2016.

9. US Food and Drug Administration. Paving the way for personalized medicine: FDA's role in a new era of medical product development. Silver Spring: US Food and Drug Administration; 2013.
10. Accord Clinical. https://www.accordclinical.com/clinical-study/types-of-clinical-trials/. Accessed 18 Oct 2017.
11. ASCO. https://www.asco.org/research-progress/clinical-trials/clinical-trial-resources/clinical-trial-design-and-methodology#Other%20Types. Accessed 18 Oct 2017.