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A Practical Guide for the Safe Implementation of Early Phase Drug Development and Immunotherapy Program in Gynecologic Oncology Practice

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Abstract

The success of targeted and immune therapies in other malignancies has led to an exponential increase in the number of active and pending clinical trials using these therapeutic approaches in patients with gynecologic cancers. These novel investigational agents are associated with unique and potentially life-threatening toxicities and many require special multidisciplinary logistical considerations. The objective of this review is to describe a practical approach for the safe implementation of targeted and immune therapies in academic gynecologic oncology practices based on our experience at M.D. Anderson Cancer Center.

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Introduction

The increased availability of immune checkpoint inhibitors (ICIs), commercialization of adoptive cell therapy, and an expanding menu of novel targeted therapies have revolutionized cancer treatment in a number of malignancies, and is ushering in an exciting new era in gynecologic cancer treatment[1]. While the use of these agents for the treatment of gynecologic cancers is largely investigational at this time, pembrolizumab (an anti-PD1 monoclonal antibody) has received FDA approval for the treatment of cervix cancer and cancers with microsatellite instability, including endometrial cancer. The inclusion of ICI in several ongoing and planned multi-institutional clinical trials means that many patients with newly diagnosed and recurrent gynecologic cancers will be receiving these agents. Further, as development of investigational agents specific to targets relevant for gynecologic cancers expands, there is a growing opportunity for implementation of first-in-human phase 1 and novel combination strategies in the Gynecologic Oncology clinic. Given that immune and targeted therapies are associated with toxicities that are distinct from traditional cytotoxic chemotherapy and may be unfamiliar to many gynecologic oncology practitioners, safe implementation requires a deliberate strategy for education of the entire clinical team including physicians, advanced practice providers, nursing staff, trainees, and, most importantly, patients. Here we describe the approach used at our institution to ensure patient safety during the roll-out of multiple clinical trials using immune and novel targeted therapies in patients with gynecologic cancers.

We focus on the core practical and programmatic aspects that were useful for the safe implementation of clinical trials at our institution and are likely to be relevant to other gynecologic oncology groups and practice settings. Readers interested in the management of toxicities such as immune-related adverse events (irAE) are referred to recently published guidelines by ASCO, ESMO, and SITC[2–4].

Creating a multidisciplinary group focused on targeted and immune therapies: the “EDDIT team”

At our institution, we made the strategic decision that safe implementation of novel therapies with new side effect profiles would require a dedicated multidisciplinary group. This group was designated the Early Drug Development and Immuno-Therapy (EDDIT) team, and included representatives from Gynecologic Oncology faculty, advanced practice providers, nursing staff, pharmacists, research coordinators, trainees and regulatory team members. The EDDIT team was charged with three main functions: first, all clinical trials in which the investigational product was either an immunotherapy drug or a drug at the early phase of development (with an incompletely characterized toxicity profile) would be conducted and overseen by the EDDIT team. This meant that while a patient was enrolled on an EDDIT-declared clinical trial, her care would be transferred to an EDDIT team faculty member if the patient’s primary gynecologic oncologist was not a part of the EDDIT team. As needed, an EDDIT faculty “call schedule” provided 24-hour coverage for the management of any patient with a serious adverse event. The second charge of the EDDIT team was to review all serious, high grade, or unexpected adverse events of EDDIT trials on a monthly basis. This

allowed the EDDIT team meeting to serve as a forum for the ongoing discussion of targeted and immunotherapy treatment related adverse events (TRAEs) and to arrive at best practices regarding their evaluation and management. The third function of the EDDIT team was to provide ongoing education and training to non-EDDIT patient care providers and trainees. This function was borne out of the recognition that, although initially patients on targeted and immunotherapy trials represent a small fraction of the overall gynecologic oncology patient population, the number of patients treated with these novel therapies would exponentially increase. Therefore, familiarity with their toxicity profiles and their management would need to be disseminated to all gynecologic oncology providers, and be incorporated into Obstetrics & Gynecology and Gynecologic Oncology training programs.

The composition and initial training of an EDDIT team

When feasible, the multidisciplinary membership of an EDDIT team should include representatives from gynecologic oncology faculty, advanced practice providers, nursing staff, pharmacists, research coordinators, trainees and regulatory / research team members. Naturally, the number of members and the exact composition of an EDDIT team will vary according to each practice setting and the anticipated volume of patients receiving targeted / immunotherapies. From a practical standpoint, it is desirable for the number of faculty and advanced practice providers to be sufficient to both accommodate the enrollment and care of the patients on EDDIT-regulated regimens, and to allow a “call system” of EDDIT physicians who can serve as a resource for other providers and trainees. However, where circumstances necessitate, the EDDIT team can include as few as one or two faculty members, but should retain its multidisciplinary composition and include pharmacy, nursing, and research staff.

An important early step after the formation of an EDDIT team is to educate and train team members in the diagnosis and management of targeted and immune therapy related adverse events. This initial education can be accomplished through a number of different approaches. For example, the Society for Immunotherapy in Cancer (SITC) sponsors a number of seminars aimed at providers wishing to gain experience in tumor immunology and immunotherapy. Alternatively, in many practice settings, access to medical oncologists or clinical trialists with experience in targeted and immune therapy trials in other departments is available. We also found it helpful to invite consultants (in particular from gastroenterology, endocrinology, pulmonary medicine, and rheumatology) with an interest in the emerging field of immune-related adverse events to give lectures and grand rounds (e.g. endocrine and gastrointestinal side effects of immune checkpoint inhibitors). For protocol specific education, the principle investigator and research team for each of the EDDIT trials prepared an educational presentation of the common, rare, and serious toxicities for the corresponding investigational product based on protocol directed management algorithms. The entire EDDIT team was invited to the protocol initiation visit and encouraged to participate on safety teleconferences for each protocol. In addition, a “quick reference card” was prepared for each trial or class of drugs (e.g. immune checkpoint inhibitors). These quick reference sheets were made accessible on common websites and in outpatient clinics, inpatient call rooms, and provider work areas.

Initial priorities for an EDDIT team

The most crucial function of an EDDIT type team is ensuring patient safety. Maximizing patient safety requires completing a number of high priority action items once the team has been assembled and baseline knowledge of common toxicities and their management has been acquired (Table 1). These initial priorities require the designation of investigational protocols or class of drugs (e.g. immune checkpoint inhibitors) as requiring EDDIT oversight. Following this, it is essential to establish appropriate referral procedures for patients treated on an “EDDIT regimen,” to enhance safety and ensure appropriate management of toxicities. Additionally, a call schedule or similar process for rapid access to expert advice in the case of serious adverse events must be developed. It is equally important to educate involved parties to ensure recognition of symptoms that may herald potentially life threatening adverse events. This includes emphasis on the education of all patient-facing healthcare personnel, especially individuals serving as the first point of contact for answering/triaging patient questions and concerns, as well as informing patients about unique aspects of potential adverse events from immune and targeted therapies. Many gynecologic cancer survivors have experience with the side effects of cytotoxic chemotherapy, and may incorrectly assume similar adverse events from immunotherapy and other biologics. Therefore, it is important to emphasize the unique nature of immune-related adverse events and their expected time course. Patients should also be educated about symptoms that should trigger prompt reporting or immediate evaluation such as bloody diarrhea or new onset cough/shortness of breath that may be indicative of immune-related colitis and pneumonitis, respectively. For first-in-human trials, it is of the utmost importance for the patient to report any adverse event immediately to allow for timely intervention, as the toxicity profile may not yet be fully understood.

The EDDIT team’s role in the recognition and management of treatment emergent adverse events

The recent publication of guidelines for the recognition and management of immune-related adverse events represents a significant step forward in enhancing the safety of these treatments[2–4]. However, these sources of theoretical knowledge do not obviate the importance of experiential knowledge in the recognition and management of immune-related adverse events. In this vein, regular EDDIT team meetings where significant adverse events are discussed enhances not only the experience of individual practitioners and ensures that all members gain experiential knowledge at the group level, especially regarding uncommon events or a small population of patients.

As with EDDIT team size and membership composition, frequency of meetings will depend on a number of variables and should be individualized for each practice setting. At M.D. Anderson, we found that convening an EDDIT team meeting on a monthly basis was optimal for our needs. During these meetings, patients with significant TRAEs are discussed in a brief case presentation format. This forum provides the opportunity to review any significant laboratory or imaging results. In addition, updates on previously discussed patients with an evolving course or treatment are also provided. These meetings are

supplemented by trial-specific safety teleconferences at intervals determined by the principal investigator and sponsor, but generally weekly or biweekly in the early phases of the trial.

The administrative portion of the meeting includes a discussion of any upcoming EDDIT protocols, development of education materials (such as upcoming didactics or “fast fact sheets” for protocols), and a discussion of if and when sufficient experience has accumulated for an EDDIT protocol to “be opened up” to enrollment by all providers. Examples of drug class and trial specific information sheets are provided in supplementary material.

The educational mission of the EDDIT

As mentioned above, one the main charges of an EDDIT team is to educate members, patient-facing staff, and patients. In addition to this early educational role, EDDIT teams are also ideally suited to provide ongoing education to trainees and non-EDDIT faculty and staff, as well as to broader audiences at regional and national meetings. Obviously, the nature and scope of the educational sessions will vary with the target audience. However, topics such as introduction to immunotherapy, immune-related side effects, adoptive cell therapy, precision medicine, PARP inhibitors and mechanisms of resistance have broad relevance and are of interest to multiple audiences. Depending on the available level of experience and expertise within the EDDIT team, the educators may be experts from other departments or institutions. At our institution, our EDDIT team was formed with the expectation that once sufficient experience with EDDIT-regulated drug regimens was gained, the use of such therapies would be liberalized to all providers. In fact, approximately 16 months after the first EDDIT meeting, the team decided unanimously that there was sufficient experience with the use of PD1- and CTLA4-targeting immune checkpoint inhibitors to expand the use these drugs to all gynecologic oncology providers. This transition required the completion of a didactic educational training session by non-EDDIT faculty. In addition, to ensure patient safety during this transition, EDDIT team members were readily available for questions or assistance with management of side effects.

Increasing safety through standardization of evaluation for patients with suspected immune- related adverse events

Although EDDIT meetings provide an excellent forum for the discussion of immune-related and targeted therapy adverse events and their management, this review is always retrospective and “after the fact.” Variability in the initial evaluation of the patients could result in delays in diagnosis, initiation of appropriate therapy, or both. Our team has recognized this as an opportunity to enhance patient safety by composing standardized order sets for the initial evaluation of patients with suspected therapy-related adverse events. Input from relevant consultants was used to develop targeted order sets for the initial evaluation of patients with common therapy related clinical presentations (Table 2, supplementary material).

It is important to note that these order sets are designed for the *initial* evaluation of a patient with possible immune or targeted therapy adverse event and are not meant to supersede the input of an expert consultant. In fact, most order sets include consultation request as one of

the initial interventions. The suggested evaluation includes the most useful laboratory and imaging studies to expedite the initial diagnostic workup, narrow the differential diagnoses, and assist the consultants and the primary team in a multidisciplinary approach for patient evaluation and management. Today, with the multiple approved indications for immune checkpoint inhibitors and many targeted therapies, many consultants are increasingly familiar with emerging TRAEs associated with these novel therapies. However, there may be practice settings where the experience with targeted and immune therapy toxicities may be more limited. Hence, we favor a multidisciplinary approach whereby the gynecologic oncology team and the consulting services together consider a broad differential diagnosis in the evaluation and management of patients with a suspected immune or targeted therapy related adverse event. In addition, consultation with protocol specific adverse event management algorithms (for patients treated as part of a clinical trial) and the ASCO, SITC, or ESMO guidelines is also encouraged.

Implementation of adoptive cell therapies for gynecologic cancers

Adoptive cell therapy (ACT, also known as adoptive cell transfer) refers to a number of different immunotherapy approaches that typically involve the acquisition of autologous immune cells (mainly T cell or NK cells) from the patient, *ex vivo* expansion, and return of the immune cells to the patient[5]. The source of the immune cells can be peripheral blood or directly from resected tumor tissue (tumor-infiltrating lymphocytes or TILs). Certain types of ACT involve genetic modification of T cells to direct the recognition of specific tumor associated antigens[5, 6]. These genetic modification techniques can produce engineered T cell receptors (TCR) that recognize tumor-derived peptides bound to the major histocompatibility complex (MHC) or chimeric antigen receptors (CAR) that render T cells able to recognize tumor surface antigens independent of MHC using an antibody-like recognition module [7, 8]. In many ACT regimens, patients undergo high dose “lympho-depleting” chemotherapy (frequently consisting of cyclophosphamide and fludarabine) during the week prior to the infusion of immune cells to decrease the number of non-specific and regulatory immune cells[9]. In addition, in some protocols T-cell infusion is followed by IL-2 because of its activation, growth, and differentiation effects on T cells, B cells, and NK cells.

Traditionally, many ACT trials were small investigator-initiated efforts conducted only at certain highly specialized centers such as the National Cancer Institute (NCI). However, with recent successes of ACT, especially CD19 CAR T-cells in B cell leukemia and multiple myeloma, this type of immunotherapy has become rapidly commercialized and clinical trials are expanding into solid tumors. Within gynecologic cancers, complete and partial responses to ACT using TIL in patients with recurrent cervical cancer have been reported[10]. This has led to intense interest in applying this type of ACT for other gynecologic cancers[11], and the development of Iovance Biotherapeutics-sponsored multi-institutional phase II clinical trial (NCT03108495). Several other ACT clinical trials using TIL and engineered TCR approaches are currently active and targeting gynecologic cancers. These developments make it likely that academic gynecologic oncology centers will be increasingly participating in ACT trials aimed at gynecologic cancers. Given the complicated logistics, high potential for toxicity, and lack of cell therapy experience in most gynecologic oncology practice

settings, it is of utmost importance to carefully consider logistical and safety concerns prior to implementing such clinical trials. Thinking about ACT trials in terms of their constituent phases can be useful for consideration of both the risks and logistics. For example, some clinical trials leave the decision of inpatient administration of lymphodepleting chemotherapy to the local PI. The type of immune cells used is also important. In general, genetically modified T cells (CAR and engineered TCRs) carry higher risks than unmodified peripheral T-cells or TIL due to the potential for unanticipated off-target effects. In addition, whether or not adjuvant cytokines such as high dose IL-2 are included significantly impacts both the risks and the logistics as it requires the inclusion of providers and inpatient units experienced with administration and monitoring required for this cytokine.

An essential prerequisite for conducting ACT trials that target gynecological cancers is the feasibility of assembling a multidisciplinary team of collaborators that includes representatives from medical oncology, stem cell transplant / cell therapy, nursing, pharmacy, and consulting services required for the assessment and management of the anticipated toxicities. Readers interested in more detailed information regarding the creation and function of such a team are referred to the recent publication by Neelapu and colleagues[12]. As with any clinical trial, a realistic assessment of feasibility is crucial. Safe implementation of ACT requires substantially more resources, range of expertise, and toxicity management capabilities compared to other types of immunotherapy (such as the use of immune checkpoint inhibitors). At a time of finite resources and uncertainty in healthcare, many academic gynecologic oncology centers will be reluctant to commit the necessary resources for enrolling a relatively small number of patients on ACT.

Summary and future directions

We have presented practical considerations for the safe implementation of novel targeted and immune therapies based on our experience over the last four years at MD Anderson Cancer Center. The discussed concepts and recommendations, however, are relevant and can be tailored to, different gynecologic oncology practice settings. The proven efficacy of immune-oncology and targeted agents in melanoma, lung cancer, and many other malignancies, and the rapidly expanding pipeline of other molecular and immunomodulatory therapeutics provides more hope than ever for patients with gynecologic cancers. This evolution requires a safe and thoughtful approach for incorporating novel and investigation therapies both in our everyday practice as well as in gynecologic oncology training programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- This review provides a system-based practical approach for the safe implementation of targeted and immune therapies
- Creation of a multidisciplinary EDDIT team can provide shared experience and enhanced patient safety
- Education of providers, staff, trainees, and patients is a key function of the EDDIT team
- Immediate access to expert advice serves to avoid delays in recognition and management of adverse events

Table 1.

A summary of the major steps in development and implementation of an Early Drug Development and ImmunoTherapy (EDDIT) team.

Major Steps	Key Considerations
1. Formation of the EDDIT team and establishment of referral procedures to EDDIT providers	Establish a charter, buy in from key stakeholders Multidisciplinary membership to include representatives from faculty, advanced practice providers, nursing, pharmacy, clinical research, and other services (if necessary) Establish regular meeting schedule and an agenda to include a review of EDDIT trials and any notable toxicities, upcoming, trials, and educational activities Availability of sufficient number of EDDIT providers to provide adequate access for the anticipated patient volume
2. Organize and educate EDDIT providers	Consider a dedicated “retreat” with invited experts in immunotherapy and targeted therapies Review of publically available toxicity management guidelines and clinical trial-specific education material including toxicity management algorithms
3. Establish and communicate procedures to provide EDDIT guidance after hours and on weekends	EDDIT call schedule or phone triage may be useful to ensure appropriate guidance is available when the primary managing provider is not an EDDIT team member Establish contingency plans for when an EDDIT faculty member may be unavailable
4. Designate investigational protocols/drug classes as requiring EDDIT oversight	Class and novelty of investigational regimen/drug and toxicity profile (e.g. immunotherapy, first in human investigational agent, novel combination)
5. Educate personnel, patients, trainees, and other providers	Educate all patient-facing healthcare personnel to ensure recognition of potential serious symptoms Educate patients on EDDIT clinical trials/therapies about the unique nature of adverse events and symptoms that should prompt provider notification or immediate medical evaluation
6. Liberalize drug class/ clinical trial to non-EDDIT providers	It is up to the EDDIT team to decide when there has been sufficient experience with a given class of drugs or investigation agent to warrant liberalizing its use to other providers Educate non-EDDIT providers and ensure assistance and guidance is available as needed

Table 2.

Suggested initial evaluation of patients presenting with symptoms suggesting immune or targeted therapy adverse events

Clinical Presentation	Laboratory Evaluation (default frequency)	Imaging Studies	Consultation(s)
Diarrhea/ Colitis	Comprehensive Metabolic Panel (daily) Complete Blood Count with Differential (daily) Stool studies (on admission) Ova & parasites, Viral studies, C. difficile DNA Assay Calprotectin Lactoferrin Thyroid stimulating hormone (on admission) C-reactive protein (on admission) Antinuclear antibody (on admission) Erythrocyte sedimentation rate (on admission)	CT abdomen pelvis with and without contrast	GI/endoscopy
Liver Dysfunction	Comprehensive Metabolic Panel (on admission) Hepatic Function Panel (daily) Hepatitis panel (on admission) ANA titer (on admission) Anti-mitochondrial antibody M2 (on admission) Anti-smooth Muscle antibody (on admission) Anti-liver/Kidney microsome type 1 Ab (anti-LKM-1) (on admission) Ceruleplasmin level (on admission) Alpha 1 antitrypsin (on admission) If not transfused within 1 month (on admission) Iron level Ferritin level Transferrin with TIBC	Liver ultrasound	GI/Hepatology
Dermatologic Toxicity	As clinically indicated	Medical Photography Request	Dermatology
Pulmonary Toxicity	As clinically indicated	CT Chest with contrast (pulmonary angiography protocol)	Pulmonary Medicine
Neurologic Dysfunction	As clinically indicated	MRI	Neurology
Renal Dysfunction	Basic Metabolic Panel- Total Calcium (daily) Urinalysis with microscopic (on admission) Urine eosinophils (on admission) Urine electrolytes and creatinine (on admission)	Renal Ultrasound	Nephrology
Bone Marrow Toxicity	Comprehensive Metabolic Panel (on admission)		Hematology

Clinical Presentation	Laboratory Evaluation (default frequency)	Imaging Studies	Consultation(s)
	Complete Blood Count with Differential (daily) Direct Antiglobulin Test (Coombs) (on admission) Haptoglobin (on admission) Hemosiderin (on admission) LDH (on admission) Peripheral Smear for review (on admission) Neutrophil Ab level 1+2+3 (on admission) Vitamin B12 level (on admission) Serum methylmalonic acid quant, (on admission) Serum copper level (on admission)		
Cardiac Toxicity	Cardiac Panel (e.g. CKMB, troponin ; on admission) Erythrocyte sedimentation rate (on admission) C-reactive protein (on admission) N-terminal Pro brain natriuretic peptide (on admission)	EKG, 12-lead Echocardiogram 2D Complete	Cardiology
Myositis or Rhabdomyolysis	Comprehensive Metabolic Panel (on admission) Creatine Kinase (on admission) Aldolase (on admission) Urinalysis with microscopic (on admission) Erythrocyte sedimentation rate (on admission) C-reactive protein (on admission) Troponin T (on admission) ANA Titer (on admission) LDH (on admission)		Rheumatology Cardiology
Endocrine (Hypophysitis)	ACTH (on admission) Cortisol, Total (Timed at 0800 or random if unwell and treatment cannot be delayed) FSH and LH Level (on admission) Prolactin (on admission) Estradiol Level (in premenopausal females on admission) TSH and Free T4 ((on admission)	Pituitary MRI with contrast	Endocrinology
Endocrine (Insulin Requiring DM)	Basic metabolic panel with calcium (on admission) C peptide (on admission) Urinalysis (on admission)		
Endocrine (Thyroid Dysfunction)	TSH, Free T4, and Total T3 (on admission) Thyroid peroxidase Ab (TPO) (on admission) Thyrotropin receptor Ab (thyrotropin binding inhibitory immunoglobulin) ((on admission)		