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REPORTING SIDE EFFECTS OF THERAPY FROM EARLY AND PIVOTAL CLINICAL TRIALS AND DEFINITION OF RECOMMENDED DOSES

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DISCLOSURES

Ahmad Awada has reported no conflicts of interest

Christian Dittrich has reported personal financial interest as Consulting and Advisory Services with Novartis, Eli Lilly, Merck, Roche and AstraZeneca. Institutional financial interest: Contracted Research with Amgen, Merck, Pierre Fabre, Pfizer, Roche, Novartis and Sanofi-Aventis

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INTRODUCTION

Reporting side effects is variable and depends on the:

Molecular family of evaluated agents (administered as single agents or in combinations)

Clinical trial phase

Disease setting

DIFFERENT CLASSES OF ANTICANCER AGENTS

Hormonal therapy

Chemotherapy

Targeted therapy

- Kinase inhibitors (KIs) / multi-KIs
- Monoclonal antibodies
- Antibody-drug conjugates

Immunotherapies

Combinations of:

- Hormonal therapy and targeted therapies
- Immunotherapies ± other agents
- Chemotherapy ± other agents

DIFFERENT TRIAL SETTINGS

Early phase trials (phases I/II)

Pivotal trials

Real-life trials

EARLY PHASE TRIALS: AIMS

To define:

- Dose-limiting toxicities (DLTs)
- Recommended dose(s) (RD) and schedule(s)
- Preliminary anti-tumour efficacy

PIVOTAL TRIALS: AIMS

To define:

- Progression-free survival, overall survival
- Quality of life
- Acute and late adverse events

DEFINING DOSE-LIMITING TOXICITIES (DLTS):

Specificities according to different agents

Classical DLTs : neutropenia-related events, non-haematologic toxicities ≥ grade (G) 3

Longer time of follow-up for immunotherapies is needed; many side effects appear after the fourth or fifth injection of immunotherapies

Modify the classical schema of 3+3 in defining DLT in some circumstances, taking into account the investigated agent, the tumour type and the setting

HETEROGENEITY IN THE DEFINITION OF DLTS

In phase I trials of molecularly targeted agents (MTAs) with potential impact on the recommended dose for phase II (RP2D)

155 phase I trials evaluating 111 different MTAs

(review of literature:

Scopus search 01/2000 – 04/2010)

- Severity of toxicity
- Duration of toxicities (minimum)
- Reversibility of toxicity
- Treatment delay
- Dose intensity reduction

COMMENT: It is important to note that the authors although reporting on heterogeneity in the definition of DLT in phase I cancer clinical trials of MTAs are not advocating for a complete standardisation of the definition of DLTs, but prefer to focus on a few main determinants as detailed above in order to allow:

A more sustainable determination of the RP2D

A better comparability of new substances in early drug development

Le Tourneau C, *et al.*, Eur J Cancer, 2011,47(10):1468-75

DLT-TARGETT – AN EORTC LED STUDY

Patients and studies:

- 54 studies / 35 agents
- February 1999 – May 2013
- Molecular targeted agents (MTAs) – monotherapy
- Solid tumours

Adverse events (AEs):

- Reported during cycles 1-6
- At least possibly related to the drug
- Not present at same or higher grade at entry

2,084 patients – 5,708 cycles – 24,918 AEs

Postel-Vinay S, *et al*, Eur J Cancer, 2014,50(12):2040-9

DLT-TARGETT – AN EORTC LED STUDY

8,812 toxicities recorded in cycle 1: 5,580 G1, 2,396 G2, 745 G3, 191 G≥4

16,106 toxicities recorded after cycle 1: 10,883 G1, 4,136 G2, 991 G3, 96 G≥4

189 (9.1%) patients experienced 300 DLTs: 5 G1, 28 G2, 225 G3, 42 G≥4

270 (90%) DLTs recorded at cycle 1

43 (80%) trials reached MTD

40 (74%) trials defined RP2D

COMMENT: In order not to delay the drug developmental process, there is an agreement that the dose escalation should primarily be based, also in the future, on data from the first cycle of therapy, but that information on chronically unbearable toxicities impacting on dose intensity should be respected from beyond the first cycle.
Comprehensive toxicity reporting beyond the DLT period is of utmost importance including all degrees of all kinds of toxicities.

Postel-Vinay S, *et al.,* Eur J Cancer, 2014,50(12); 2040-2049

DOSE EXPANSION COHORTS IN PHASE I TRIALS

Goal: Optimising the volume and quality of data at the RP2D

Endpoints: Safety, tolerability, efficacy, pharmacokinetics (PK), pharmacodynamics (PD)

Patient enrichment

- 24%: Expansion cohort reported
  More likely if: more recent, multicentre, molecularly targeted drug
- 74%: Objectives reported: Safety (80%), efficacy (45%), PK (28%), PD (23%)
- 13%: RP2D modified
- 54%: New toxicities reported
- 11%: New anticancer activity reported

COMMENT: Expansion cohorts in phase I are of high impact on the fine-tuning of the RP2D and therewith the further development of a drug.

Manji A, *et al.,* J Clin Oncol, 2013, 31(33); 4260-4267

REPORTING SIDE EFFECTS: LEARNING FROM PRIOR EXPERIENCES FROM PHASE I TO PHASE III OF SELECTED AGENTS OF DIFFERENT CLASSES OF ANTI-NEOPLASTIC AGENTS

The commented findings in the next slides are to be considered in documenting and reporting side effects of future clinical trials

EARLY PHASE TRIALS OF SELECTED AGENTS IN SOLID TUMOURS

Phase I/II trial of enzalutamide in prostate cancer

Letrozole + everolimus phase I in metastatic breast cancer

T-DM1 phase I in metastatic breast cancer

Phase I trial of sunitinib in advanced malignancies

Phase I nab-paclitaxel in advanced non haematologic malignancies

Phase I pegylated doxorubicin in advanced solid tumours

Phase I/II ipilimumab in recurrent melanoma

Phase I nivolumab in solid tumours

Phase I study of nivolumab and ipilimumab in recurrent melanoma

PIVOTAL TRIALS OF SELECTED AGENTS IN SOLID TUMOURS

Enzalutamide *versus* placebo in advanced prostate cancer

BOLERO 2: Exemestane ± everolimus in metastatic breast cancer

EMILIA TRIAL: T-DM1 *versus* lapatinib + capecitabine in metastatic breast cancer

Sunitinib *versus* interferon alfa in advanced renal cell carcinoma

Nab-paclitaxel *versus* paclitaxel in advanced breast cancer

Ipilimumab in melanoma

Nivolumab in melanoma

Ipilimumab *versus* nivolumab *versus* combination in melanoma

HORMONAL THERAPY ± TARGETED THERAPY IN ADVANCED SOLID TUMOURS

ENDOCRINE THERAPY ALONE

Phase I/II enzalutamide trials in prostate cancer

140 patients

Dose-escalation cohorts of three to six patients and given an oral daily starting dose of enzalutamide 30 mg (n=3), 60 mg (27), 160 mg (28), 240 mg (29), 360 mg (28), 480 mg (22), and 600 mg (3)

DLT for sustained treatment at 240 mg; RD: 160 mg per day

- The most common grade 3-4 adverse event was dose-dependent fatigue (11%)

COMMENT: Study including high number of patients to better document the safety of recommended dose (and secondary the efficacy)

Scher HI, *et al.*, Lancet, 2010;375(9724):1437-46

ENZALUTAMIDE IN ADVANCED PROSTATE CANCER

Rate of adverse event twice compared to placebo

Equivalent incidence of grade ≥ 3 side effects with enzalutamide (45%) *versus* placebo (53%)

Cardiac toxicity evaluation by EKG: no clinically relevant changes

- Specific side effects: 5/800 cases of seizures. Predisposing factors: brain metastases, lidocaine administration and brain atrophy

COMMENT: The phase III trial better defined the side effects (the most frequent or the rare ones) of enzalutamide

Scher HI, *et al.*, N Engl J Med 2012; 367:1187-1197

ENDOCRINE THERAPY AND TARGETED THERAPY

Phase I letrozole + everolimus in breast cancer

18 patients in two cohorts:

- Cohort 1 (n=6): letrozole 2.5 mg + everolimus 5 mg
- Cohort 2 (n=12): letrozole 5 mg + everolimus 10 mg

Absence of DLT in cohort 1

Expansion of the cohort 2 to 12 patients for additional safety and pharmacokinetics

- Most common adverse events were stomatitis (50%), fatigue (44%), anorexia and/or decreased appetite (44%), diarrhoea (39%), headache (33%) and rash (33%)

COMMENT: 1 DLT in cohort 2 (a grade 3 thrombocytopenia), but high percentage of non-DLTs were cumbersome for the patients and should be taken into account in the definition of the recommended dose

Awada A, *et al.,* Eur J Cancer, 2008; 44(1):84-91

BOLERO-2 IN METASTATIC LUMINAL BREAST CANCER

Exemestane ± everolimus in hormone pre-treated advanced luminal breast cancer

Serious adverse events 23% (combination) *versus* 11%

Adverse events all grade (grade 3/4): Stomatitis 56% (8%), hyperglycaemia 13% (5%), pneumonitis 12% (3%)

Discontinuation 19% versus 4%

7 deaths attributed to adverse events!

COMMENT: Taking into account the percentage of serious adverse events, discontinuation rate and the number of toxic deaths led to the conclusion that the selected dose of everolimus was not optimal

ANTIBODY-DRUG CONJUGATES

ANTIBODY-DRUG CONJUGATE

T-DM1 phase I in advanced breast cancer

24 patients

T-DM1 escalating dose from 0.3 mg/kg to 4.8 mg/kg

Common drug-related adverse events included grade ≤2 thrombocytopenia, elevated transaminases, fatigue, nausea, and anaemia. No grade >1 vomiting, alopecia, or neuropathy events and no cardiac effects requiring dose modification were reported

- DLT at 4.8 mg/kg was transient thrombocytopenia
- RP2D was 3.6 mg/kg

COMMENT: Dose and schedule were proved to be valid in later phases of clinical trials (Emilia, Theresa, …)

Krop IE, *et al.,* J Clin Oncol, 2012; 30(26):3234-41

EMILIA TRIAL IN HER-2 POSITIVE ADVANCED BREAST CANCER

Serious adverse events: 15.5% in T-DM1versus 18% in lapatinib-capecitabine

Most frequent grade 3-4 adverse events of T-DM1: thrombocytopenia (13%) and elevated serum concentrations of aspartate aminotransferase (4%)

Management of thrombocytopenia feasible by reducing the dose in 28% patients (discontinuation in 2%)

Cardiac toxicity (3 patients with less than 40% of left ventricular ejection fraction)

Death: 1 attributed to T-DM1 (due to metabolic encephalopathy)

COMMENT: Recommended dose and schedule based on early trials proved to be valid in phase III trials

Verma S, *et al*., N Engl J Med 2012; 367:1783-1791

MOLECULAR TARGETED THERAPIES IN ADVANCED SOLID TUMOURS

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MULTI-TARGETED KINASE INHIBITOR

Phase I trial of sunitinib

28 patients

Dose escalation from 50 mg every other day to 150 mg/d

RD: 50 mg/d (4 weeks on, 2 weeks off)

Toxicities at the RD: sore mouth, oedema, thrombocytopenia, hair discoloration, and yellow coloration of the skin

DLTs: reversible grade 3 fatigue, grade 3 hypertension and grade 2 bullous skin toxicity

COMMENT: The recommended dose and schedule of sunitinib were based on a limited number of patients

Faivre S, *et al.*, J Clin Oncol 2006, 24 (1):25-35

ADVERSE EVENTS OF SUNITINIB IN ADVANCED RENAL CELL CARCINOMA

In phase III studies

Treatment-related adverse events percentage were reported

Adverse events occurring at least in 10% of the patients

Most frequent adverse events (grade 3/4): diarrhoea 61% (9%), fatigue 54% (11%)

Specific adverse events: cardiac and thyroid adverse events

Percentage of dose reduction in 50% patients; 19% discontinuation due to adverse events

Treatment-related deaths were reported

COMMENT: The percentage of dose reduction and discontinuation in phase III trials illustrated well the non optimal dose and schedule selection based on few patients in the phase I programme.

Motzer RJ, *et al.*, J Clin Oncol 2009;27(22):3584-90

NEW FORMULATIONS OF CYTOTOXIC AGENTS

NEW FORMULATION OF PACLITAXEL

Phase I nab-paclitaxel

39 patients

2 cohorts: heavily pre-treated or patients with limited prior treatments

80 to 200 mg/m^2 once a week for 3 weeks followed by 1 week rest period

DLT: grade 4 neutropenia and grade 3 peripheral neuropathy

MTD: 100 mg/m^2 for heavily pre-treated and 150 mg/m^2 for patients with limited pre-treatment once a week for 3 weeks followed by 1 week rest period

COMMENT: Important to define the adverse events, recommended dose and schedule in heavily *versus* less pre-treated patients

Nyman DK, *et al*., J Clin Oncol 2005, 23(31): 7785-7793

NAB-PACLITAXEL *VERSUS* PACLITAXEL

In phase III metastatic breast cancer

Compliance to the treatment was 96% in nab-paclitaxel *versus* 90% in standard paclitaxel

AE-treatment discontinuation, dose reduction and delays as well as QOL were reported

Hypersensitivity reaction evaluation and management are detailed

The most frequent side effects are summarised according to the grade in a table

Comparison between the side effects of standard paclitaxel and nab-paclitaxel has been performed

Treatment related deaths are indicated

COMMENT: Randomised clinical trial is the only way to optimally compare the adverse events between standard anti-cancer agent and new formulations of the same agent

Gradishar WJ, *et al.*, J Clin Oncol, 23(31): 7794-7803

NEW FORMULATION OF DOXORUBICIN

Two complementary phase I studies of pegylated liposomal doxorubicin

56 patients

Two separate phase I studies:

- Starting dose of the first one: 20 mg/m^2; the second one: 60 mg/m^2
- Both studies ➔ cohorts of 3 patients and redosing every 3 to 4 weeks
- 50 mg/m^2 every 3 weeks explored and 60 mg/m^2 every 4 weeks expanded

DLT: stomatitis (high single dose) and hand-foot syndrome (repetitive dosing)

RP2D: 50 mg/m^2 every 4 weeks

COMMENT: This study illustrated well the importance to define the optimal dose in repetitive cycles rather than in first cycle (different DLTs)

Uziely B, *et al.*, JCO, 1995, 13(7): 1777-1785

CHECKPOINT INHIBITORS IN ADVANCED MALIGNANCIES

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CHECKPOINT INHIBITOR

Phase I/II ipilimumab in recurrent melanoma

Single doses of ipilimumab up to 20 mg/kg (group A, n=34)

Multiple doses up to 5 mg/kg (group A, n=30)

- ➔ No DLTs

Multiple doses up to 10 mg/kg (group B, n=24)

- ➔ 6 DLTs / 23 patients

Grade 3 or 4 immune-related adverse events (irAEs) were observed in 14% of patients (12 of 88 patients), and grade 1 or 2 irAEs were seen in an additional 58%.

COMMENT: Toxicities were related to the dose and the frequency of the administrations

Weber JS, *et al.,* J Clin Oncol 2008, 26(36): 5950-5956

ADVERSE EVENTS OF IPILIMUMAB

In phase III studies of advanced melanoma

Adverse events were listed in a table (all grades, grade 3 and grade 4)

Immune related side effects were observed in 60% of patients

The median time to resolution of immune-related adverse events is noted

Management modalities and outcomes of immune-related side effects were reported

Also reported are residual effects and ongoing events of adverse effects in patients after a follow-up of two years

Treatment related deaths are indicated

COMMENT: Adverse event issues are well reported in this trial and in particular the residual effect after a long period of follow-up of the observed adverse events

Hodi FS, *et al.,* N Engl J Med 2010; 363:711-723

PHASE I NIVOLUMAB IN ADVANCED SOLID TUMOURS

304 patients

Nivolumab (0.1−10 mg/kg IV, every two weeks) during dose escalation and/or cohort expansion

Drug-related side effects in 72% (220/304); G3/G4 side effects in 15% (45/304) of patients

Pneumonitis occurred in 3% (10/304), including G3/G4 in 1% (3/304), resulting in 3 deaths early in the trial, which led to increased clinical monitoring and an emphasis on establishing management algorithms

RP2D: 3 mg/kg every two weeks

COMMENT: The important number of patients in this dose-finding study and expansion phase permitted to define the dose/schedule of nivolumab as well the side effects at short and long term administrations

Topalian SL , ASCO Annual Meeting 2013. J Clin Oncol 31, 2013 (suppl; abstr 3002)

ADVERSE EVENTS OF NIVOLUMAB PHASE III TRIAL

In metastatic melanoma

The incidence of adverse events was 74.3% (G3/G4: 11.7%)

The most common adverse events were fatigue (in 20% of patients), pruritus (in 17%), and nausea (in 16.5%)

The percentage of patients who discontinued was 7%. No deaths were attributed to study-drug toxicity in either group

Selected adverse events — defined as those with a potential immunologic cause — were analysed according to organ category

The majority of selected adverse events of grade 3 or 4 resolved quickly with a delay in the study treatment, steroids administration, or both

COMMENT: No unexpected adverse events were observed in the phase III programme

Robert C, *et al.,* N Engl J Med 2015; 372:2521-2532

CHECKPOINT INHIBITORS COMBINATIONS

Phase I nivolumab plus ipilimumab in melanoma

86 patients

5 concurrent cohorts with different doses and 2 sequential cohorts with different doses

Adverse events: mainly immune-related adverse events

DLT: grade 3 or 4 asymptomatic elevated lipase (cohort 3)

Patients who discontinued treatment: 11/56 (20%) in concurrent cohorts

COMMENT: This study determined the modality of administration of two agents concurrently or sequentially. The side effects were possibly underestimated due to relatively limited number of patients

Wolchock JD, *et al.*, N Engl J Med 2013; 369:122-133

IPILIMUMAB AND NIVOLUMAB COMBINATION IN ADVANCED MELANOMA

The percentage of treatment-related adverse events of any grade is 96%, the most common adverse events being diarrhoea

Incidence of patients who discontinued the treatment due to adverse events is 36%; diarrhea and colitis being the most frequent

Immune-related adverse events are detailed with their percentage

Management modalities of adverse events and resolution rates for selected adverse events are presented

COMMENT: The true incidence and types of side effects were better documented in the pivotal study

Larkin J, *et al.,* N Engl J Med 2015; 373:23-34

SELECTED REAL-LIFE TRIALS

Exemestane-everolimus in metastatic breast cancer

Sunitinib in metastatic renal cell carcinoma

Pegylated liposomal doxorubicin in metastatic breast cancer

EXEMESTANE-EVEROLIMUS

In real-life advanced breast cancer

Most frequent adverse events reported - all grades (grade 3/4): stomatitis 56% (10.4%), hypercholesterolaemia 47.4% (0%), hyperglycaemia 36.4% (6%), pneumonitis 16% (2%)

Stomatitis was the main cause of interruption/discontinuation (10.4% definitively stopped and 52% temporarily interrupted)

52% interrupted ➔ 61% reduced the dose to 5 mg and 39 resumed at the same dose

COMMENT: Interruption and discontinuation in real-life trial reveal that the recommended dose from phase I trial was probably not adequate

Forcignanò RC, *et al*., Cancer Research, 2016; 76 (4)Suppl., Abstr., 38th Annual CTRCAACR San Antonio Breast Cancer Symposium; December 2015; San Antonio, TX

SUNITINIB

In real-life in metastatic renal cell carcinoma

More cardiac side effects (34%) reported in real-life than in clinical trials

Besides the cardiac side effects, safety and efficacy of sunitinib for metastatic renal-cell carcinoma were similar to those noted in the phase III trials

COMMENT: This study reported that some specific side effects are more frequently detected in real-life (cardiac side effects !)

Schmidinger M, *et al.,* J Clin Oncol 2008, 26:5204-5212.
Gore ME, *et al.,* Lancet Oncol 2009;10(8):757-63

PEGYLATED LIPOSOMAL DOXORUBICIN

In real-life metastatic breast cancer

Left ventricular ejection function was not reduced by more than 15%

The major side effects (grade 4) were haematological toxicity (anaemia, leukopenia, and thrombocytopenia), hand-foot syndrome, and stomatitis

COMMENT: Real-life trials can confirm the results obtained in phase III trials

Rom J, *et al*., Anticancer Drugs, 2014; 25(2):219-24

PATIENT-REPORTED OUTCOME (PRO) ASSESSMENT

In reporting side effects

Thoughtful incorporation of patients into clinical trials by using PRO assessment

PRO-CTCAE (common terminology criteria for adverse events) a new tool for assessment of PRO side effects being developed by the FDA

Potential use of PRO measurement in early phase clinical trials (exploration of safety, dose optimisation) and late phase trials (selection of informative adverse events)

Prevent the under-reporting of adverse events and better concordance with real-world results

Kluetz PG, Chingos DT, *et al.*, Am Soc Clin Oncol Educ Book. 2016;35:67-73

PRO-CTCAE: DATA COLLECTION

Various methods to collect data: paper, phone, web, …

Location: in the clinic (paper or table computer) or between visits (web, automated telephone)

Compliance of the patient to PRO-CTCAE is essential: reminders and back-up data collection is a must

Basch E, *et al*., J Clin Oncol. 2016;34:557-65

CTCAE *VERSUS* PRO-CTCAE: THE EXAMPLE OF MUCOSITIS

CTCAE					
Adverse Event	Grade				
	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	-

PRO-CTCAE
Please think back over the past 7 days:
What was the **severity** of your MOUTH OR THROAT SORES at their WORST? None / Mild / Moderate / Severe / Very severe
How much did MOUTH OR THROAT SORES **interfere** with your usual or daily activities? Not at all / A little bit / Somewhat / Quite a bit / Very much

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CONCLUSIONS – REPORTING SIDE EFFECTS IN EARLY PHASE TRIALS

The recommended dose schedule for later phases is usually determined in these trials based on the reported side effects at the first cycles

The recommended doses are usually based on DLT (grade 3 or more side effects), but high percentage of non-DLTs (grade 2) should be taken into consideration in the definition of recommended dose and schedule

Side effects are regularly underestimated in some early phase trial. More patients treated in early phase trials, e.g. in expansion cohorts, might minimise this important issue

CONCLUSIONS – REPORTING SIDE EFFECTS IN PIVOTAL TRIAL

The frequency of all grade and grade 3/4 side effects, the rate of treatment discontinuation/interruption and treatment related deaths are usually reported in pivotal trials

Pivotal trials confirm the side effects described in early phase trials but often reveal the real wider panel of side effects not necessarily detected earlier, due to the limited experience (fewer patients, limited number of cycles)

CONCLUSIONS – REPORTING SIDE EFFECTS IN REAL- LIFE TRIALS

Real-life trials can confirm the characteristics of side effects obtained in phase III trial and can stress on specific side effects more frequently observed in real-life (less selected patients than in pivotal trials)

Thank you!