Comparison of study designs, objectives and results of Phase I trials with cytotoxic versus non-cytotoxic anticancer agents

Lindy Bosch, Edwin Klumper and Raymond Hoffmans

Specialized Medical Services-oncology BV (SMS-oncology), Science Park 408, 1098 XH Amsterdam, The Netherlands
www.sms-oncology.com, +31 20 435 0580, l.bosch@sms-oncology.com, r.hoffmans@sms-oncology.com

Introduction

Cytotoxic anticancer agents are designed to kill tumor cells by interfering with cell division mechanisms. In contrast, non-cytotoxic anticancer agents intend to inhibit cancer growth by targeting specific proteins or signaling pathways or by activating the immune system. We investigated whether these different modes of action are reflected in study designs, objectives and results of Phase I studies.

Materials and methods

We conducted a PubMed search for full length English articles published in 2012 and 2013 describing completed single-agent Phase I studies in adult patients with solid tumors. Parameters were extracted, entered into a database and used to compile summarizing tables.

Results

We retrieved 191 single agent Phase I reports (Table 1). Non-cytotoxic agents were investigated in almost twice as many studies compared to cytotoxic agents.

Table 1: Cytotoxic vs non-cytotoxic agents

	Cytotoxic N (%)	Non-cytotoxic N (%)	Total N (%)
# studies	64 (34%)	127 (66%)	191 (100%)
# patients	2044 (29%)	5007 (71%)	7051 (100%)

Trial characteristics

The percentage of studies investigating a single tumor indication was larger with non-cytotoxic agents. The main routes of administration (RoA) are intravenous (IV) and per os (PO). In three quarter of the cases IV is the RoA for cytoxic agents and in half of the cases PO is the RoA for non-cytotoxic agents (Table 2).

Table 2: Patient population and RoA

	Cytotoxic N (%)	Non-cytotoxic N (%)
Patient population		
Single tumor type	7 (11%)	37 (29%)
Mixed tumor types	57 (89%)	90 (71%)
Route of administration		
Intravenous	50 (78%)	30 (24%)
Per os	11 (17%)	61 (48%)
Intradermal	-	13 (10%)
Subcutaneous	-	7 (5%)
Intravenous + per oral	1 (2%)	4 (3%)
Intramuscular	-	4 (3%)
Intratumoral	1 (2%)	3 (2%)
Intravesical	-	3 (2%)
Intraperitoneal	1 (2%)	1 (1%)
Subconjunctival	-	1 (1%)

Studies with non-cytotoxic agents had a slightly increased sample size, study duration and enrollment time compared to studies with cytotoxic agents. There was no difference in the number of sites that participated in the studies (Table 3).

Table 3: Trial characteristics

	Cytotoxic N (%)	Non-cytotoxic N (%)
Patients per study		
# studies	64	127
Mean # patients (SD)	31,9 (19,3)	39,4 (44,8)
Median # patients (range)	28 (5-108)	22 (4-296)
Sites per study		
# studies	46	84
Mean # sites (SD)	2,5 (1,5)	2,3 (1,9)
Median # sites (range)	2 (1-9)	2 (1-11)
Study duration		
# studies	11	23
Mean # months (SD)	28,2 (12,7)	33,0 (11,2)
Median # months (range)	*30 (6-42)*	*34 (12-55)*
Enrollment time		
# studies	33	56
Mean # months (SD)	24,5 (17,4)	26,8 (13,6)
Median # months (range)	25 (3-63)	22 (5-80)

Trial design

In studies with cytotoxic agents, on average 1 extra dose level was tested compared to studies with non-cytotoxic agents (Table 4).

Table 4: Dose escalation dose levels

	Cytotoxic N (%)	Non-cytotoxic N (%)
Dose levels		
# studies	64	127
Mean # dose levels (SD)	6,2 (4,1)	5,2 (3,8)
Median # dose levels (range)	5 (1-23)	4 (1-21)

In the fast majority of studies a rule-based design instead of a model-based design was used for dose escalation. From the rule based designs, the traditional 3+3 dose escalation design is most popular for both cytotoxic as well as non-cytotoxic agents (Table 5).

Table 5: Dose escalation design

	Cytotoxic N (%)	Non-cytotoxic N (%)
Rule-based design		
3+3	41 (64%)	63 (50%)
Accelerated titration	13 (20%)	16 (13%)
Pharmacologically Guided Dose Escalation (PGDE)	-	2 (2%)
Model-based design		
Time to Event Continual Reassessment Method (TITE-CRM)	1 (2%)	1 (1%)
Escalation With Overdose Control (EWOC)	-	1 (1%)
Continuous Reassessment Method (CRM)	-	1 (1%)
Other	5 (8%)	28 (22%)
No dose escalation	5 (6%)	15 (12%)

Trial objectives

The primary objectives in both groups were mainly related to safety and tolerability. The main difference in secondary objectives was the increased use of pharmacodynamic endpoints with non-cytotoxic agents (Table 6).

Table 6: Objectives

	Cytotoxic N (%)	Non-cytotoxic N (%)
Primary objective		
# studies	44	79
MTD	29 (66%)	30 (38%)
Safety	13 (30%)	46 (58%)
Tolerability	11 (25%)	24 (30%)
DLT	12 (27%)	16 (20%)
Toxicity	4 (9%)	8 (10%)
PK	9 (20%)	18 (23%)
RP2D	13 (30%)	13 (16%)
PD	3 (7%)	4 (5%)
Efficacy	3 (7%)	3 (4%)
Secondary objective		
# studies	39	75
Efficacy	28 (72%)	54 (72%)
PK	28 (72%)	37 (49%)
PD	9 (23%)	47 (63%)
Safety	11 (28%)	16 (21%)
Tolerability	4 (10%)	10 (13%)
MTD	1 (3%)	4 (5%)
Toxicity	4 (10%)	-
DLT	1 (3%)	2 (3%)
RP2D	3 (8%)	3 (4%)

Trial results

The maximum tolerated dose (MTD) was more often reached in studies with cytotoxic agents (Table 7).

Table 7: Maximum tolerated dose

	Cytotoxic N (%)	Non-cytotoxic N (%)
MTD reached		
Yes	44 (69%)	42 (33%)
No	9 (14%)	38 (30%)
Not applicable	11 (17%)	47 (37%)

Studies with non-cytotoxic agents reported slightly better objective response rate, stable disease rate and disease control rate than studies with cytotoxic agents (Table 8).

Table 8: Efficacy

	Cytotoxic N (%)	Non-cytotoxic N (%)
Objective Response Rate		
# studies	63	112
Mean % (SD)	4,5 (11,9)	6,1 (11,8)
Median % (range)	0 (0-80)	0 (0-60)
Stable Disease		
# studies	59	111
Mean % (SD)	30,0 (15,3)	33,5 (22,3)
Median % (range)	30 (0-68)	30 (0-88)
Disease Control Rate		
# studies	61	111
Mean % (SD)	33,6 (17,4)	39,3 (22,1)
Median % (range)	33 (0-80)	38 (0-96)

Conclusion

There are differences in study designs, objectives and results for studies with cytotoxic compared to non-cytotoxic agents. The main difference between the two groups is the use of a single indication (11% vs 29%), the route of administration (IV vs PO), the use of PD endpoints (23% vs 63%) and the establishment of the MTD (69% vs 33%).

References

A list with the references of the 191 articles can be provided upon request.