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ORIGINAL ARTICLE

Safety and efficacy of NAD depleting cancer drugs: results of a phase I clinical trial of CHS 828 and overview of published data

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Abstract
Purpose Depletion of cellular nicotinamide adenine dinucleotide (NAD) by inhibition of its synthesis is a new pharmacological principle for cancer treatment currently in early phases of clinical development. We present new and previously published data on the safety and efficacy of these drugs based on early clinical trials.
Methods A phase I clinical trial of CHS 828 in patients with advanced solid tumours was performed. Published clinical trials on NAD depleting drugs for cancer treatment were summarised for safety and efficacy.
Results Seven patients with previously treated solid tumours received oral administration of CHS 828 in the dose range 20–80 mg once weekly for 3 weeks in 4 weeks cycles. Toxicity was dominated by gastrointestinal symptoms including nausea, vomiting, diarrhoea, constipation, subileus and gastric ulcer. One patient had thrombocytopenia grade 2. There were two cases each of grade 3–4 hyperuricemia and hypokalemia. Safety and efficacy of the NAD depleting drugs CHS 828 and FK866 have been reported from four phase I clinical trials, including a total of 97 patients with previously treated solid tumours. Outstanding toxicity reported was thrombocytopenia and various gastrointestinal symptoms. No objective tumour remission has been observed in the total of 104 patients treated in the above early trials.
Conclusions Critical toxicity from NAD depleting cancer drugs to consider in future trials seems to be thrombocytopenia and various gastrointestinal symptoms. Efficacy of NAD depleting drugs when used alone is expected to be low.

Keywords Cancer · NAD depletion · Phase I clinical trial · CHS 828 · FK866 · GMX1777

Introduction

Recent progress in tumour cell biology has formed the basis for development of new cancer drugs, notably the ‘targeted drugs’ that interfere with the intracellular signal pathways considered to provide the phenotypical characteristics of many tumour cell types [1]. Several such drugs are already approved and in routine clinical use but despite their provision of major break-through in the treatment of some cancer types, treatment progress in the major cancer diagnoses has been limited and there is need for mechanistically new drugs [2].

New promising cancer drugs should preferably be based on drug targets that are preferentially expressed in cancer compared with normal cells. In this respect, most recent efforts have tried to target signal transducing cell-surface receptor tyrosine-kinases [1, 2]. A more general abnormality of most tumour cells, observed almost 100 years ago and which is the basis for the use of positron emission tomography in cancer diagnostics, is the altered tumour cell metabolism known as the “Warburg phenomenon”,

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characterised by increased glycolysis producing excess lactate also under aerobic conditions [3, 4]. This phenomenon may be advantageous to the tumour cell but could also be exploited therapeutically by development of drugs inhibiting glycolysis [4].

Another approach also taking advantage of the metabolic properties of tumour cells is to deplete the cells from nicotinamide adenine dinucleotide (NAD) [5]. NAD is an important co-factor in the oxidative phosphorylation chain as well as a substrate for enzymes involved in genomic stability, apoptosis, cell signalling, stress tolerance and metabolism [5–7]. NAD depletion will lead to, e.g. lowered ATP levels and inhibition of poly(ADP-ribose) polymerases (PARPs) that are involved in DNA repair [5, 8–10]. Since tumour cells have increased PARP activation, high ATP demands and inefficient ATP production through the Warburg effect, tumour cells would be expected to be more sensitive than normal cells to inhibition of NAD synthesis [5]. Thus, NAD synthesis inhibitors could provide an advantageous therapeutic ratio as cancer drugs, as supported by preclinical data [5, 10–13]. Furthermore, such drugs seem suitable for combination with cancer therapy producing DNA damage, e.g. alkylating drugs and radiotherapy [8, 14–17].

Two NAD depleting drugs have so far reached the early clinical phases of development as cancer drugs. These are FK866 and CHS 828 (now under development as the prodrug GMX1777 for intravenous, iv, administration [15]) which are both inhibitors of nicotinamide phosphoribosyl transferase (Nampt), a crucial step in the synthesis of NAD from nicotinamide [6, 18].

Since these drugs represent a new class of cancer agents, it was considered relevant to summarise the experience so far on their clinical safety profile as well as efficacy. Especially when considering new trials in which NAD depleting drugs are to be combined with other cancer drugs or radiotherapy, it is important to have knowledge on the adverse effects profile to avoid serious overlapping toxicity. In this light, we here report data from a phase I clinical trial of CHS 828 and an overview of the safety and efficacy of FK866 and CHS 828 as reported in the literature.

Materials and methods

Phase I clinical trial of CHS 828

This was a prospective single centre open label non-comparative phase I clinical trial performed at Uppsala University Hospital from 2000 to 2001. The primary objective was to determine a recommended phase II dose (RPTD) employing a once weekly dosing. Secondary objectives were to assess tumour responses and pharmacokinetics (PK) under fasting and non-fasting conditions. The study was approved by the Medical Product Agency in Sweden and by the Uppsala University ethics committee. All patients gave a written informed consent to participate in the study. The study was carried out according to the International Conference on Harmonisation Guidelines for Good Clinical Practice. The study was closed prematurely since further development of per oral CHS 828 was stopped due to development of a CHS 828 prodrug for iv infusion (GMX1777).

Key inclusion criteria were histologically proven solid tumour for which no satisfactory therapy was available or had failed, age 18–75 years, ECOG performance status of $\leq$2 and written informed consent. Key exclusion criteria were previous cancer therapy within 4 weeks of baseline visit, life expectancy of <3 months, leukocytes $<3 \times 10^9$/l, platelets $<100 \times 10^9$/l, S-creatinine >1.5× upper normal limit (UNL), ASAT/ALAT >3× UNL (5× in the case of liver metastasis) and bilirubin >2× UNL.

CHS 828 was manufactured by Nova Laboratories Ltd. and was certified and supplied by LEO Pharma, Ballerup, Denmark. The dosage form was 10 and 50-mg gelatin capsules for oral administration. The treatment schedule for all patients was drug administration once weekly for 3 weeks with start of a new cycle every 4 weeks. A range of predefined doses from 20 to 200 mg once weekly for 3 weeks was used for dose escalation or reduction and the starting dose for the first patient was 40 mg. Toxicity was scored according to the National Cancer Institute Common Toxicity Criteria (CTC, version 2.0). The starting dose was to be reduced for the next patient in the case of dose limiting toxicity (DLT; nausea/vomiting CTC grade 4, diarrhoea $\geq$grade 3, thrombocytopenia grade 4, leukopenia grade 4, other adverse events $\geq$grade 3), unchanged in the case of dose holding toxicity (DHT; nausea/vomiting CTC grade 3, diarrhoea grade 2, thrombocytopenia grade 3, leukopenia grade 3, other adverse events grade 2) and escalated in the absence of DHT and DLT. Only safety during the 1st cycle was considered for these dose changes.

Once a DLT in the 1st cycle was observed, the dosing for subsequent patients were computer based using the Continual Reassessment method with a Likelihood approach (CRML) to target a DLT level of 20% at RPTD. No dose increase was allowed for the individual patient. Treatment was to be given for three cycles or until intolerance, disease progression or patient wish for withdrawal. Adverse events were assessed every 3–4 days as of haematological status whereas biochemistry was assessed weekly. In the case of measurable disease, this was to be evaluated by imaging every 3rd cycle according to WHO response criteria.

Blood for measurement of serum concentrations of CHS 828 was sampled 10 times up to 24 h after drug intake at days 1 and 15 in cycle 1 and 6 times up to 12 h after drug intake at days 1 and 15 in cycles 2 and 3. All patients received the study drug under fasting conditions in the 1st cycle. At baseline, patients were randomized to receive the study drug under fasting conditions or after a standardised breakfast in cycle 2 with cross-over to fasting/standardised breakfast in cycle 3. The limited amount of data obtained prohibit clear conclusions on CHS 828 PK for the schedule used and, thus, only individual patient T_{max} and C_{max} values in cycle 1 will be reported here.

Retrieval of published clinical trial data on NAD depleting drugs

The data bases PubMed, Google Scholar and Scirus and the American Society of Clinical Oncology abstract database were searched using the above drug names as well as "NAD depletion, Nampt, nicotinamide phosphoribosyl transferase" combined with "cancer and clinical trial" and relevant reports on drug safety in clinical trials in cancer patients were retrieved and results were tabulated. Toxicity in all trials was scored according to the National Cancer Institute Common Toxicity Criteria (CTC, version 2.0), except for the trial so far only reported in the abstract format in which this was not detailed.

Results

Results of the phase I clinical trial of CHS 828

The trial recruited eight heavily pretreated patients with gastrointestinal or ovarian cancer and detailed patient characteristics are presented in Table 1. Patient 4 deteriorated rapidly after inclusion and never received study drug. Patients were treated at CHS 828 doses of 20, 40, 60 or 80 mg once weekly for 3 weeks in 4 weeks cycles and the number of cycles administered ranged 1–3. No dose changes were done in individual patients.

A RPTD could not be defined in accordance with the protocol due to the premature trial closure. However, drug related toxicity was observed at 40, 60 and 80 mg (Table 2). Clinical toxicity was dominated by gastrointestinal problems with nausea, vomiting, diarrhoea, constipation and subileus and there was one case of gastric ulcer. One patient experienced grade 2 thrombocytopenia and another grade 3 anaemia. There were two cases of grade 4 hyperuricemia and two cases of hypokalemia of grade 3 and 4, respectively. Reasons for study withdrawals were progressive disease or medical deterioration in four patients and study drug related adverse events in four.

No clinical or objective signs of tumour remission were observed. Median T_{max} was 1.5 h (range 1–6) with limited variation within cycle 1 (Table 1). C_{max} in cycle 1 ranged between 5 and 2,542 ng/ml and seemed related to

Table 1 Patient characteristics and CHS 828 dosing and basic pharmacokinetics

Gender/patient number	Age	Diagnosis	ECOG performance status at baseline	Previous lines of chemo-therapy	Dose (mg) once weekly for 3 weeks/ no of cycles	T_{max} (h) and C_{max} (ng/ml) after dose intake days 1 and 15 in course 1
Male/1	55	Rectal cancer	1	4	40/3	1/1 226/482
Female/2	70	Pancreatic cancer	1	2	60/2	1/1.5 845/756
Male/3	73	Rectal cancer	2	3	80/1	1.5/4 1,049/306
Female/4	61	Gall bladder cancer	2	2	None[a]	ND
Male/5	62	Colon cancer	2	4	20/1	1.5/1 120/61
Male/6	58	Gastric cancer	1	1	40/3	ND/1.5 5/9
Female/7	71	Ovarian cancer	2	3	40/2	2/4 178/784
Female/8	51	Ovarian cancer	2	5	80/1	6/ND 2,542/ND

no Number, *ECOG* Eastern Cooperative Oncology Group, *ND* not done

[a] This patient deteriorated rapidly after study inclusion and never got study drug

Table 2 Toxicity by worst grade ≥ CTC grade 2 considered at least possibly related to the study drug and clinically significant changes from baseline in biochemistry/haematology

Patient number	Laboratory toxicity	Clinical toxicity	DLT/reason for withdrawal
1	None	Vomiting gr 2	Fatigue/PD
		Fatigue gr 3	
		Anorexia gr 2	
		Diarrhoea gr 3	
		TIA gr 3	
		Weight loss gr 2	
2	Hypokalemia gr 4	Nausea gr 3	Hypokalemia, subileus, fatigue/unacceptable AEs
		Vomiting gr 3	
		Constipation gr 2	
		Subileus gr 3	
		Fatigue gr 3	
3	Hyperuricemia gr 4	Vomiting gr 2	Hyperuricemia, fatigue, subileus, gastric ulcer/unacceptable AEs
	Anaemia gr 3		
	Thrombocytopenia gr 2	Constipation gr 2	
		Subileus gr 3	
		Gastric ulcer gr 3	
		Stomatitis gr 2	
		Fatigue gr 2	
4	NA	NA	NA/medical deterioration
5	None	None	None/medical deterioration
6	Anaemia gr 3	Uretritis gr 2	Anaemia/completion of protocol
7	Hyperuricemia gr 4	Vomiting gr 2	Hyperuricemia, hypokalemia, dehydration/unacceptable AEs
	Hypokalemia gr 3		
	Anaemia gr 2	Diarrhoea gr 2	
		Nausea gr 2	
		Fatigue gr 2	
		Dehydration gr 3	
		Abdominal pain gr 2	
8	None	None	None/medical deterioration

CTC Common toxicity criteria, *gr* grade, *DLT* dose limiting toxicity, *TIA* transient ischaemic attack, *PD* progressive disease, *AE* adverse event, *NA* not applicable

dose but showed considerable within and between patient variability.

Overview of safety and efficacy of NAD depleting cancer drugs

Five publications, including two conference abstracts, reporting adverse effects and efficacy from NAD depleting drugs in early clinical trials were retrieved and are summarised in Table 3. They were all phase I clinical trials including a total of 97 patients with advanced mostly heavily previously treated malignancies with no standard therapy available. The route of administration of the NAD depleting drug was per oral in two and by iv infusion in two trials. No objective tumour responses were observed in any of the trials.

Table 4 summarises the most common and outstanding toxicity observed which was considered study drug related. Thrombocytopenia grade 3–4 was observed in all trials with frequencies ranging from 2 to 20% of the cycles. Anaemia was mostly grade 2 but severe, i.e. grade 3–4, occasionally occurred. Grade 4 leukopenia was only observed in one of the trials with a frequency of 3% and there was no case of infection with neutropenia reported in any trial.

Gastrointestinal toxicity, mostly nausea, vomiting and diarrhoea, was reported with frequencies up to 37% of cycles for grade 2 and up to 6% for grade 3–4. Gastrointestinal toxicity was seemingly less frequent in the trials with iv compared with oral administration and was not concluded to be dose-limiting in the iv trials. Fatigue and

Table 3 Overview of early clinical trials of NAD depleting drugs

Author/reference	Clinical phase/tumour types	Drug	No of pts (f/m) included and median age	Schedule	No of courses	RPTD
Hovstadius et al. [19]	Phase I/advanced solid tumours	CHS 828	16 (10/6) 58 y	PO 5 d q 4 w	Mean 3	20 mg/d for 5 d q 4 w
Ravaud et al. [20]	Phase I/advanced solid tumours	CHS 828	38 (14/24) 56 y	PO 1 d q 3 w	Mean 3	420 mg once q 3 w
Holen et al. [21]	Phase I/advanced resistant solid tumours	FK866	24 (12/12) 61 y	96 h cont iv inf q 28 d	Median 2	0.126 mg/m^2/h 96 h cont iv inf q 28 d
Pishvaian et al. [22, 23]	Phase I/advanced malignancies	GMX1777 (CHS 828 prodrug)	19 (8/11) 57 y	24 h cont iv inf q 3 w	Mean 2	140 mg/m^2 cont iv inf q 3 w

No number, *f* female, *m* male, *RPTD* recommended phase II dose, *PO* per oral, *q* every, *w* week, *y* year, *d* day, *cont* continuous, *iv* intravenous, *inf* infusion, *h* hour

Table 4 Summary of drug related worst grade adverse events CTC grades 3–4 and grade 2 with incidence of ≥20%

Adverse event	Grade	Study drug/administration/reference			
		CHS 828 po 5 d q 4 w [19]	CHS 828 po once q 3 w [20]	FK866 96 h iv inf q 28 d [21]	GMX1777 24 h iv inf q 3 w [22, 23][a,b]
Thrombo-cytopenia	3	20	7	6	-
	4	–	1	2	2
Leukopenia	3	2	1	23	-
	4	–	3	–	–
Anaemia	2	14	20	21	–
	3	2	6	–	–
	4	–	1	2	–
Nausea	2	37	7	4	–
	3	2	2	4	–
Vomiting	2	20	10	–	–
	3	4	2	–	–
	4	–	1	–	–
Diarrhoea/dehydration	2	24	3	–	–
	3	6	2	–	4
	4	–	1	–	–
Fatigue	3	2	7	2	–
Arthralgia/myalgia	3	–	1	–	2
DLTs highlighted in report		Thrombocyto-penia, thrombosis, esophagitis, diarrhoea, constipation	Thrombocyto-penia mucositis, diarrhoea, haematuria, leukopenia,	Thrombocyto-penia	Thrombocyto-penia, gastrointestinal haemorrhage, skin rash

Only events reported in at least two trials were included. Data extracted from the published reports and reported as per cent of treatment cycles (Approximation for the FK866 trial, originally reported per patient). Last row details the DLTs highlighted in the study reports

CTC Common toxicity criteria, *q* every, *w* week, *iv* intravenous, *inf* infusion

[a] Toxicity <grade 3 not specified

[b] Toxicity based on complementary information in the two reports

arthralgia/myalgia grade 3 were reported up to 7% in 2–3 of the trials.

Among less prominent adverse events localised mucositis grade 2–3 was reported with a frequency of 2–18% in the trials using oral drug administration. Some cases of oesophagitis and haematuria in these trials might represent similar toxicity. Gastrointestinal bleeding and melena were reported as single adverse events in the GMX1777 trial.

These adverse events may also indicate toxic effects on mucous membranes and the gastrointestinal toxicity mentioned above seemingly also support the notion of mucous membrane toxicity from NAD depleting drugs. GMX1777 was associated with skin rash grade 3–4 in 2–18% of cycles but only after repeated drug administration.

With respect to changes in biochemistry considered at least possibly drug related there were frequencies up to 10% of grade 2–3 hyperglycaemia, hypokalemia, hypoalbuminaemia and elevated ALP in the trials with iv administration. Thrombocytopenia was considered DLT in all trials. In addition, various types of gastrointestinal toxicity were highlighted as DLT in three out of the four trials.

Discussion

NAD depletion is an interesting pharmacological principle for cancer treatment since it theoretically could provide an advantageous therapeutic ratio with tumour cells being more sensitive than normal cells. Experimental in vitro and in vivo data provide support to this notion [10, 12, 13]. Furthermore, since NAD is involved in DNA repair processes, NAD depletion would be an interesting principle for combinations, especially with DNA damaging drugs or radiotherapy [8, 14, 17].

At present there are two drugs in early clinical testing with NAD depletion by inhibition of Nampt as their principle mechanism of action, CHS 828/GMX1777 and FK866 [6, 18]. A total of 104 patients, including those in the phase I clinical trial presented here, have been exposed to these drugs as reported in literature.

There are clearly conceptual difficulties in the interpretation of phase I clinical trials, especially with respect to efficacy but also to tolerance. The main reasons are the mostly low number of patients treated, the inherent problem of appropriate drug dosing and scheduling in early clinical trials and the inclusion of patients with therapy refractive disease and expected poor tolerance due to advanced disease and previous therapy. Still, the pattern of adverse events was quite similar between the trials, and we think it is possible to make reasonable conclusions on the tolerance to this mechanistically new class of cancer drugs. This tolerance pattern needs to be considered in future clinical trials, especially in the design of trials with combinations of a NAD depleting drug and other cancer drugs or radiotherapy.

Despite premature closure our phase I trial still provided useful data on the clinical and laboratory tolerance profile of CHS 828 as reported here. CHS 828 tolerance was generally in agreement with that previously published, indicating that CHS 828 toxicity is largely unrelated to schedule when CHS 828 administrated the oral route. However, thrombocytopenia was seemingly less conspicuous than previously observed. This might be due to dose or schedule or the inclusion of patients in our trial with expected poor tolerance to drugs producing gastrointestinal toxicity, i.e. patients with advanced gastrointestinal or ovarian cancer. In this trial, we observed two cases each of severe hypokalemia and hyperuricemia. These adverse effects might be secondary to the gastrointestinal problems or might represent a specific but fairly low frequent toxicity induced by CHS 828. Most probably, the deviation in our trial from the tolerance pattern previously published relates to the low number of patients included in our trial and their baseline characteristics rather than to treatment schedule and dosing. In our study, these were somewhere in between those used in the studies by Hovstadius and Ravaud et al. and that showed fairly consistent patterns of adverse events [19, 20].

Thrombocytopenia was an outstanding toxicity in the previously published trials and was not obviously related to route of administration or schedule. The thrombocytopenic episodes observed were generally short but the combination of a NAD depleting drug with thrombocyte or generally bone marrow suppressive drugs might be problematic.

The clinical toxicity from the NAD depleting drugs seems dominated by various gastrointestinal symptoms, frequently observed also with many standard cancer drugs. Considering also the possible mucous membrane toxicity from the NAD depleting drugs, combinations with many standard drugs could be problematic. This might also be the case for the use of radiotherapy simultaneously with CHS 828 or FK866 if the irradiated volume includes the abdomen or mucous membranes located elsewhere. This is problematic since a NAD depleting drug is theoretically promising for combination with radiotherapy. Still, a beneficial therapeutic window might be found if the doses of the NAD depleting drug and radiotherapy are appropriately adjusted.

The adverse effect profile of mainly thrombocytopenia and some gastrointestinal toxicity was also recently observed in a not yet published phase II trial of CHS 828 in nine patients with chronic lymphocytic leukaemia using the oral 5 days every 4 weeks schedule (Hovstadius et al., to be published). Since the gastrointestinal toxicity might be handled by prophylactic anti-emetics and anti-diarrhoea drugs and might be less problematic when drug administration is by the iv route, the thrombocytopenia seems to be the outstanding tolerance problem from NAD depleting drugs when used alone.

There is too limited data to allow for clear-cut conclusions on comparisons between CHS 828 and FK866 and between various routes of administration and schedules. Still, tentative conclusions would be that iv compared with oral administration is better tolerated with respect to gastrointestinal toxicity, that the adverse event profile from oral

administration of CHS 828 is unrelated to schedule and that thrombocytopenia is a class characteristic of these drugs. Again, these conclusions need to be studied further in future clinical trials.

Our trial provided too little data on CHS 828 PK to allow for clear conclusions on variation over cycles and effect of drug administration in the fasting/non-fasting condition. However, T_{max} seemed unrelated to dose whereas C_{max} tended to be dose-related. There were considerable within and between patient variations in drug exposure but C_{max} was not obviously related to adverse events. These findings are largely in agreement with summary PK data from 70 patients exposed to oral CHS 828 in four clinical trials (Leo Pharma, data on file). In this summary median T_{max} was 2 h and median $T_{1/2}$ 2.5 h, the inter- and intra-patient coefficient of variation for AUC and C_{max} approximately 130 and 60%, respectively, and adverse events could not reliably be predicted from drug exposure. Development of an iv CHS 828 prodrug to reduce PK variability and gastrointestinal toxicity thus seems warranted.

Although objective tumour remissions are known to be infrequent in phase I trials with new cancer drugs, the absence of tumour remissions among the 104 patients exposed in the early trials is disappointing, especially in the light of treatment algorithms in several trials allowing for accelerated dose escalation to avoid non-therapeutic drug dosing. Furthermore, there were also no clinically relevant therapeutic effects in the not yet published phase II trial in chronic lymphocytic leukaemia mentioned above. Although it is certainly too early to conclude that NAD depleting drugs are inactive as single drugs, it is speculated that it might be more fruitful to look for beneficial combinations with this new class of cancer drugs based on synergistic effects from therapies producing DNA damage and NAD depletion.

In conclusion, NAD depletion is theoretically an interesting approach for the development of more effective cancer drugs now in early clinical development. The limited experience so far indicates that thrombocytopenia and gastrointestinal toxicity need to be considered in the design of future clinical trials with these drugs, both when used as single drugs and when combined with drugs or radiotherapy expected to produce therapeutic synergy.

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Conflict of interest statement None.

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