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REVIEW – CLINICAL ONCOLOGY

Clinical pharmacology and clinical trials of ribonucleotide reductase inhibitors: is it a viable cancer therapy?

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Abstract

Purpose Ribonucleotide reductase (RR) enzymes (RR1 and RR2) play an important role in the reduction of ribonucleotides to deoxyribonucleotides which is involved in DNA replication and repair. Augmented RR activity has been ascribed to uncontrolled cell growth and tumorigenic transformation.

Methods This review mainly focuses on several biological and chemical RR inhibitors (e.g., siRNA, GTI-2040, GTI-2501, triapine, gemcitabine, and clofarabine) that have been evaluated in clinical trials with promising anticancer activity from 1960's till 2016. A summary on whether their monotherapy or combination is still effective for further use is discussed.

Results Among the RR2 inhibitors evaluated, GTI-2040, siRNA, gallium nitrate and didox were more efficacious as a monotherapy, whereas triapine was found to be more efficacious as combination agent. Hydroxyurea is currently used more in combination therapy, even though it

is efficacious as a monotherapy. Gallium nitrate showed mixed results in combination therapy, while the combination activity of didox is yet to be evaluated. RR1 inhibitors that have long been used in chemotherapy such as gemcitabine, cladribine, fludarabine and clofarabine are currently used mostly as a combination therapy, but are equally efficacious as a monotherapy, except tezacitabine which did not progress beyond phase I trials.

Conclusions Based on the results of clinical trials, we conclude that RR inhibitors are viable treatment options, either as a monotherapy or as a combination in cancer chemotherapy. With the recent advances made in cancer biology, further development of RR inhibitors with improved efficacy and reduced toxicity is possible for treatment of variety of cancers.

Keywords Ribonucleotide reductase · Progression-free survival · Clinical trial · Efficacy · Toxicity · Response rate

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Introduction

The field of oncology progressed last several years with the advances in targeted cancer therapy. In targeted therapy, the specific proteins involved in tumor growth and suppression are selectively inhibited by small molecule drugs or biologics. A number of anticancer drugs, such as imatinib (Cohen et al. 2005), trastuzumab (Blumenthal et al. 2013), temsirolimus (Hudes et al. 2007) and bortezomib (Kane et al. 2007), have been approved by FDA based on targeted therapy approaches in a wide variety of cancers. Despite these advances in targeted therapy, agents with novel mechanisms of action are continually sought to overcome resistance associated with these agents and for improved clinical outcomes. Ribonucleotide reductases (RR) represent a class

of enzymes which have been exploited for these purposes based on their role in DNA synthesis and repair (Elledge et al. 1992). The inhibitors targeting these enzymes have been marketed as cancer chemotherapeutic agents such as gemcitabine (Oettle et al. 2007), fludarabine (Rai et al. 2000) and hydroxyurea (Platt 2008). Even though these drugs have been available for several years, there has been a recent interest in RR inhibitor-based combination therapies to overcome the resistance associated with classical anticancer regiments and also targeting additional mechanisms for improved clinical benefit. In particular new antisense agents and siRNA inhibitors of RR have shown potential in this regard and have reached to clinical trial stage. This review will cover some of the advances made in the RR inhibitors and the clinical pharmacology and clinical trials of these agents until year 2016.

RR—background and biochemistry

RR proteins are the class of enzymes that are found in all eukaryotes (yeast, algae, plants and mammals), some prokaryotes and viruses. They catalyze the reduction of purine and pyrimidine ribonucleotide to their corresponding deoxyribonucleotide (Elledge et al. 1992), which are the basic units of DNA replication and repair in eukaryotic cells.

A unique feature of the RR enzyme is that the reduction of ribonucleotide proceeds via a free radical mechanism of action (Fontecave et al. 1990; Eklund et al. 1997; Stubbe and Riggs-Gelasco 1998). All RR enzymes consist of two components, namely a radical generator and a reductant (Kolberg et al. 2004). The radical generator is buried deep inside the protein and differs between various subtypes of RR enzymes, whereas the reductant component is somewhat similar between the RR enzymes.

Based on the type of metal cofactors utilized for catalytic activity, RR enzymes are divided into three classes (Reichard 1993b; Stubbe and van Der Donk 1998), namely Class I, Class II and Class III. Class I and Class II RR enzymes require a diferric-tyrosyl radical (Sjoberg and Reichard 1977) and adenosylcobalamin (Blakley 1965; Beck et al. 1966), whereas Class III RR enzymes require glycyl radical cofactor (Reichard 1993a) for catalytic activity. Once the substrate binds, these cofactors initiate the free radical reaction and generate an essential thiyl radical. Subsequently, the free radical is transferred to the active site via the set of hydrogen atoms residing in the enzyme where the substrate is oxidized to its radical form and is subsequently reduced at the C2′ position of the ribose sugar of the ribonucleotide (Licht et al. 1996; Persson et al. 1997). The energy source for the reduction mainly comes from NADH and intermediately by the reductant. The reductants for the Class I, Class II and Class III RR enzymes are theioredoxin/glutaredoxin, thioredoxin and formate, respectively.

Class 1 RR is further subdivided into three subclasses namely Class Ia, Ib and Ic, depending on their sequence similarity and allosteric regulation pattern (Jordan et al. 1994). Human RR enzymes belong to Class 1a. The structure of Class I RR enzyme consists of a large R1 subunit and a small R2 subunit. These subunits associate to form an active heterodimeric tetramer (Fairman et al. 2011). R1 contains the active site along with allosteric sites which mediates the regulation of substrate specificity and activity (Uhlin and Eklund 1994) including the essential cysteine designated to become the thiyl radical, while R2 subunit contains the cofactor diferric-tyrosyl radical which is transferred to cysteine on R1 protein to initiate the catalytic process.

RR inhibitors

RR enzymes play an important role in cell proliferation and are responsible for maintaining an optimal supply of deoxyribonucleotide triphosphates (dNTPs) required for DNA synthesis and repair. Higher RR activity is associated with malignant transformation and cancer metastasis. Inactivation of RR in cells leads to decreased intracellular concentration of dNTPs, inhibition of DNA synthesis and repair, cell cycle arrest and apoptosis (Albert and Gudas 1985; Guo et al. 2016). Higher RR activity is associated with increased malignancy and invasive potential, especially in RR2 cells (Fan et al. 1996; Zhou et al. 1998). The increased need for dNTPs for cancer cells compared to normal cells makes the inhibition of RR a more attractive target for anticancer therapy.

The expression of P53R2 gene, a R2 homolog (~80% homology) that is identified in human cells (Tanaka et al. 2000), is induced by ultraviolet light, γ-irradiation or DNA damaging agents in a p53 dependent manner. P53R2 gene acts by supplying dNTPs for DNA synthesis and repair in G0/G1 cells in p53 dependent manner (Yamaguchi et al. 2001) as compared to S/G2 phases for RR2. Thus, inhibitors of P53R2 can potentially represent important clinical utility.

RR inhibitors are broadly divided into two categories, according to the target and mechanism of action, namely protein inactivators and gene expression regulators. Protein inactivators are mostly small molecule analogs, while gene expression regulators are mostly large molecules. Both these class of agents inhibit either RR1 or RR2 subunits (Table 1). RR1 inhibitors inhibit the active site or induce allosteric malfunction. RR2 inhibitors impair the required diiron tyrosyl radical center through radical scavengers or iron chelators. Other classes of inhibitors include the

Table 1 Biochemical classification of RR inhibitors

RR1 inhibitors	RR2/P53R2 inhibitors
Protein inactivators	Protein inactivators
1. Substrate analogs	1. Radical scavengers
(a) Gemcitabine: cytidine-5′-triphosphate synthase inhibitor	(a) Hydroxyurea
(b) Tezacitabine: purine nucleoside analogue	(b) Didox: hydroxy benzohydroxamic acid derivative
(c) DMDC: deoxycytidine analogue of cytosine arabinoside	(c) Trimidox: hydroxy benzohydroxamic acid derivative
(d) Cytarabine: analog of human cytosine deoxyribose (deoxycytidine)	(d) Nitric oxide
	(e) Alkoxyphenols
2. Allosteric effector analogs	2. Iron chelators
(a) Fludarabine: purine analog (also inhibits DNA polymerase)	(a) Triapine: heterocyclic carboxaldehyde thiosemicarbazone derivative
(b) Cladribine: purine analog (mimics nucleoside adenosine and inhibits adenosine deaminase)	(b) Desferrioxamine: hexadentate chelator
(c) Clofarabine: purine nucleoside antimetabolite	(c) PIH
3. Bivalent nucleotide inhibitor	3. Iron mimics
(a) ADP-S-HBES-S-dGTP-adenine derivative	(a) Gallium maltolate
	(b) Gallium nitrate
4. R1 Sulfhydryl group inactivators	
(a) Caracemide hydroxamic acid derivative	
(b) Cisplatin	
5. Redox mediator	
(a) Motexafin gadolinium	
Gene expression regulators	Gene expression regulators
1. R1 antisense inhibitor	1. R2 antisense inhibitor
(a) GTI-2501	(a) GTI-2040
	2. siRNA inhibitor

polymerization inhibitors which prevent the formation of RR holoenzyme.

There have been some excellent reviews regarding the RR inhibitors covering it more from chemistry, biochemistry and drug discovery perspective with limited emphasis on clinical trials (Shao et al. 2006a; Cerqueira et al. 2007; Chapman and Kinsella 2011; Moorthy et al. 2013; Shao et al. 2013; Aye et al. 2015). This review highlights the RR inhibitor area from clinical pharmacology and clinical trials perspective. The review also discusses whether the RR inhibitors are effective as monotherapy or in combination.

Current RR2 inhibitors in clinical trials

GTI-2040

GTI-2040 is a 20-mer antisense nucleotide developed against the R2 component of RR enzyme for the treatment of cancer. Preclinical studies have demonstrated that GTI-2040 decreased the mRNA and protein levels of RR2 in various cancer types including colon tumors, pancreatic tumors, liver tumors, lung tumors, breast tumors, renal tumors, ovarian tumors, melanoma, brain glioblastoma-astrocytoma, prostatic tumors and cervical tumors in nude

and/or severe combined immunodeficient mice (Lee et al. 2003). Various phase I/II/III trials have already been completed or currently underway for these agents.

In the phase I dose escalation studies for the treatment of advanced solid tumors (Desai et al. 2005), the GTI-2040 is well tolerated in patients with manageable toxicity when given as a single agent. The recommended phase II dose of 185 mg/m^2/day. GTI-2040 was also tried as a combination therapy in a number of clinical trials. The objective was to induce the down regulation of RR through GTI-2040 and also potentiate or increase the cytotoxicity of the drugs in the combination regimen.

A phase I trial was conducted combining GTI-2040 with high-dose cytarabine (*ara-C*) for myeloid leukemia (Klisovic et al. 2008). Twenty-three patients were given GTI-2040 by i.v. infusion in escalating doses along with high dose cytarabine. Eight out of twenty-three patients achieved complete response with an overall response rate of 35%. Bone marrow RR2 protein levels were reduced by (>50%) after 24 and 120 h. Neurotoxicity was the dose limiting toxicity. Based on these results phase II trials are currently underway.

A phase I study of GTI-2040/oxaliplatin and capecitabine was conducted as a part of California Cancer Consortium study for advanced metastatic solid tumors

(Shibata et al. 2009). Six patients were subjected to treatment with GTI-2040 along with capecitabine and increasing doses of oxaliplatin. Two of the six patients had a stable disease at maximum tolerated dose and one patient had a partial response to therapy at a higher dose level. Dose limiting toxicities were mainly hematologic in nature. In this small patient sample there was no clear decrease in RR expression in peripheral blood mononuclear cells during treatment, however, the treatment was found to be efficacious.

A phase I/II study of GTI-2040 with capecitabine was carried out in renal cell carcinoma patients (Stadler et al. 2008). Phase II studies carried out with a MTD of 185 mg/m^2 of GTI-2040 demonstrate that out of eighteen fully measurable response out of twenty-six, only one patient responded. Peripheral mononuclear blood cells also showed variable RR2 expression. Further evaluation of this combination therapy is not indicated.

A phase I/II study of GTI-2040 with docetaxel for advanced non-small cell lung cancer (NSCLC) was carried out (Leighl et al. 2009). Twenty-nine patients were treated with GTI-2040 and docetaxel by i.v. infusion. Twelve of the eighteen patients in phase II study had stable disease as their response. Two patients developed grade 4/5 neutropenia. For NSCLC patients, median time to progression was 3.2 months and median survival time was 7.9 months. No correlation between peripheral RR2 expression levels and response were observed. Overall, efficacy of the combination therapy does not seem to be superior as compared to docetaxel alone.

Phase II study of GTI-2040 in combination with docetaxel and prednisolone for castration resistant prostate cancer was carried out with twenty-two patients (Sridhar et al. 2011). One partial response and twelve stable diseases were recorded for sixteen patients. A confirmed prostate-specific antigen (PSA) response was seen in nine out of twenty-two patients (41%). Grade 3 toxicities such as neutropenia, leucopenia and lymphopenia were observed. Median time to progression was 4.1 months and median survival time was 13.2 months. Only two patients showed reduced RR2 levels. Overall, the combination therapy did not increase the clinical benefit as compared to docetaxel and prednisolone combination and hence further study of this dose and schedule was not recommended.

Overall, these studies indicate that GTI-2040 is efficacious as a monotherapy but showed mixed results when used as combination therapy. Phase I studies of GTI-2040 with cytarabine and oxaliplatin/capecitabine is promising but most of the phase II studies were not efficacious. Even though GTI-2040 have to be administered via a continuous infusion (Desai et al. 2005), the specificity of RR2 inhibition makes it an attractive target to pursue.

siRNA

Another potential mechanism of selective inhibition of RR2 is to knockdown the RR2 gene which is over-expressed in tumor cells. There has been a growing interest in the treatment of cancer cells using small interfering RNA (siRNA). It has been demonstrated that sequence specific, siRNA-mediated inhibition of RR2 effectively blocked cell proliferation and induced G1/S-phase cell cycle arrest both in vitro and in vivo (Avolio et al. 2007; Davis et al. 2010). In cynomolgus monkeys no hematopoietic toxicity was observed after administration of siRNA (Heidel et al. 2007). The nanoparticle formulation of siRNA, CALAA-01 is currently in phase I trials (Davis 2009) and is shown to synergistically increase the activity of alkylating agent temozolomide in melanoma cell lines. Because of the nanoparticle formulation, selective delivery of siRNA to the tumor tissue is possible, while minimizing non-specific effects caused by small molecules as compared to antisense agents. The siRNA agents holds more promise as therapeutic agent with minimal toxicity and further studies in humans are under progress.

Triapine

Triapine is a potent RR2 inhibitor which works by quenching the tyrosine radical and forming chelate with iron in the catalytic site (Cory et al. 1995; Shao et al. 2006b). Triapine is very potent in inhibiting the RR enzyme as well as tumor cell growth. The compound is also active against hydroxyurea resistant tumors (Yen et al. 1994; Finch et al. 2000). Triapine has been evaluated in various clinical trials as a monotherapy and in combination with other drugs.

Triapine has been evaluated as a single agent in several phase I and phase II studies (Table 2) which includes different types of cancer such as advanced leukemia (Giles et al. 2003), advanced solid tumors (Murren et al. 2003), advanced hematologic malignancies (Gojo et al. 2007), head and neck squamous cell carcinoma (Nutting et al. 2009) and renal cell carcinoma (Knox et al. 2007). In most of the cases no complete response or partial response is observed with phase I studies of triapine. Results of the phase II studies show that the response rate (5.9%) and overall survival were similar to other agents used for the current or recurrent head and neck squamous cell carcinoma (Glick et al. 1980; Catimel et al. 1994; Nutting et al. 2009). In case of renal cell carcinoma even though the response rate is 7%, grade 3 and grade 4 neutropenias were seen in 79% of patients which led to the termination of the study.

Triapine was also tried as a combination therapy to act synergistically or potentiate the activity of chemotherapeutic agents such as fludarabine for refractory acute leukemia

Table 2 Triapine clinical trials

Drug name	Trial design	Indication	Phase	Outcomes	Dose limiting toxicity (grade 3 or 4 or 5)	References
Triapine	Single agent	Advanced leukemia	I	No OR	Hepatotoxicity	Giles et al. (2003)
	Single agent	Advanced solid tumors	I	No OR	Leucopenia	Murren et al. (2003)
	Single agent	Advanced hematologic malignancies	I	No OR	Not met	Gojo et al. (2007)
	Single agent	Head and neck squamous cell carcinoma	II	PR: 1/32 SD: 8/32 RR: 5.9% PFS: 5.6 TTP: 3.9	Neutropenia	Nutting et al. (2009)
	Single agent	Renal cell carcinoma	II	PR: 1/15 SD: 7/15 RR: 7% OS: 14.6 TTP: 3.6	Neutropenia	Knox et al. (2007)
	Combination with fludara-bine	Refractory acute leukemia and aggressive myelo-proliferative disorder	I	CR: 2/24 PR: 3/24 RR: 21%	Fever and metabolic acidosis	Karp et al. (2008)
	Combination with doxo-rubicin	Advanced solid tumors	I	SD: 3/20	Febrile neutropenia, thrombocytopenia and myelosuppression	Schelman et al. (2009)
	Combination with gem-citabine	Advanced solid tumors	I	PR: 1/30 SD: 15/30 OS: 7.9 RR: 53%	Thrombocytopenia, leuko-peia and neutropenia	Mortazavi et al. (2013)
	Combination with high dose cytarabine	Advanced myeloid leu-kemia	I	PR: 1/15 CR: 1/15 RR: 13.33%	Methemoglobinemia	Odenike et al. (2008)
	Combination with fludara-bine	Refractory acute myeloid leukemia and aggres-sive myeloproliferative disorder	II	CR: 9/37 PR: 4/37 HI: 5/37 OS: 6.9 RR: 49%	Acidosis, kidney injury, respiratory distress syndrome and sepsis.	Zeidner et al. (2014)
	Combination with gem-citabine	Non-small cell lung cancer	II	SD: 4/15 OS: 5.4 TTP: 1.8	Methemoglobinemia, leucopenia	Traynor et al. (2010)

CR complete response, *PR* partial response, *HI* hematologic improvement, *RR* response rate (CR + PR + HI) in %, *SD* stable disease, *OR* objective response, *PFS* median progression-free survival (in months) unless otherwise indicated, *OS* median overall survival (in months), unless otherwise indicated, *TTP* median time to progression (in months), unless otherwise indicated in reviews

and aggressive myeloproliferative disorder (Karp et al. 2008), doxorubicin for advanced solid tumors (Schelman et al. 2009) or gemcitabine for non-small cell lung cancer (Ma et al. 2008) and advanced solid tumors (Mortazavi et al. 2013). Especially, the combination with fludarabine is very promising for aggressive myeloproliferative disorder with the response rate of 79% (as compared to the overall response rate of 21% including refractory acute leukemia). A phase II confirmatory study of the combination of triapine and fludarabine in patients with aggressive myeloproliferative neoplasms and secondary acute myeloid leukemia (Zeidner et al. 2014) demonstrated an overall response rate of 49% (18/37), with a complete remission rate of 24% (9/37). The median overall survival

of both overall responders and complete responders were 10.6 months. Although cases of grade 4 acidosis, kidney injury and grade 5 respiratory distress syndrome and sepsis were observed, the combination therapy was found to be very promising. In the case of combination therapy with doxorubicin, since clinical response was seen in melanoma and prostate cancer patients, further phase II studies were recommended (Schelman et al. 2009). Triapine combination with gemcitabine is associated with toxicity such as methemoglobinemia and hypoxia which could limit its use in further clinical development for non-small cell lung cancer (Ma et al. 2008). A phase 1 clinical study with triapine infusion in combination with fixed dose rate gemcitabine in advanced solid tumor patients is associated with grade 4

thrombocytopenia, leukopenia and neutropenia with 3% of the patients having partial response and 50% of the patients with stable disease for an overall response rate of 53% (Mortazavi et al. 2013). Similar efficacy data were obtained by Traynor et al. (2010), along with the observation that patients with *MDR1* variant genotypes of C3435T experienced superior overall survival compared to non-variants. In a phase I study of triapine in combination with high-dose cytarabine for advanced myeloid leukemia, a response rate of 13.33% was observed. Methemoglobinemia was the dose limiting toxicity at a triapine dose of 100 mg/m^2 and the combination showed promise for further phase II trials (Odenike et al. 2008). Based on the published clinical trials it appears that triapine shows promise when combined with agents such as fludarabine, high dose cytarabine, gemcitabine and doxorubicin than when used as monotherapy alone.

Apart from drugs, triapine (24–72 mg/m^2) was also tried as a combination with radiation therapy in patients with locally advanced pancreatic cancer (Martin et al. 2012) in a phase I study. 50% of the patients had stable disease and 17% achieved partial response. 92% of the patients experienced freedom from local tumor progression. The remaining patients who experienced progression, metastasis developed without local progression. No major dose limiting toxicities were observed.

Didox and trimidox

Didox and trimidox are two excellent radical scavengers that form complexes with iron thereby inhibiting RR2. They have also shown to be more effective than hydroxyurea for inhibiting the growth of various tumor cell lines (Elford et al. 1979; Szekeres et al. 1994b, 1995). Didox have been evaluated in various phase I and phase II trials. Didox when administered as a single agent short infusion (Veale et al. 1988) was well tolerated in phase I dose escalation studies. Even though no objective response was found in terms of efficacy, it was investigated further due to its potent enzyme inhibition and manageable toxicity. When the infusion time was increased to 36 h in another phase I study (Carmichael et al. 1990), no objective response was recorded, but the compound was found to be safe for further investigation.

A phase II study of didox conducted in 14 patients with breast cancer, did not demonstrate any efficacy response in patients (Rubens et al. 1991). However, the toxicity was minimal. Based on these observations further Phase III study of didox were not carried out. Nevertheless, didox was found to overcome radiation-induced Bcl-2 expression in p53 null prostate cancer cells (Inayat et al. 2002).

Didox was also evaluated as a combination therapy. When combined with carmustine, an alkylating agent, didox showed synergistic activity in 9L glioma cells and DAOY human medulloblastoma cells for brain tumor (Horvath et al. 2004a, b). It was also shown to act synergistically in combination with temozolomide in brain tumor cell lines (Figul et al. 2003). Didox was also shown to exhibit synergistic activity with melphalan, an alkylating agent, for the treatment of multiple myeloma (Raje et al. 2006). Didox also increased the antitumor effect of cidofovir-induced apoptosis in Epstein–Barr virus positive nasopharyngeal carcinoma xenografts (Wakisaka et al. 2005). However, most of these combination agent studies were carried out in cell lines and have not been demonstrated in clinical trials.

Trimidox, another hydroxyl-benzohydroxamic acid derivative have not been evaluated in clinical trials. Nevertheless, trimidox has shown to induce apoptosis and activate caspases in HL-60 promyelocytic leukemia cells (Fritzer-Szekeres et al. 2000). It also exhibits antiproliferative effects in human ovarian carcinoma cells (Rosenberger et al. 2000). Trimidox has, especially shown to act synergistically with a number of anticancer agents such as tiazofurin (Szekeres et al. 1994a), adriamycin (Fritzer-Szekeres et al. 1998), streptozotocin (Iyamu et al. 2000), *ara-C* (Fritzer-Szekeres et al. 2002), cisplatin and cyclophosphamide (Novotny et al. 2006) for the treatment of leukemia.

Gallium compounds

Gallium compounds have long known to concentrate in cancer tissues and the radioactive isotope of gallium (gallium-67) is used in gallium scanning (a diagnostic method) to detect tissues in the body affected by cancer. Proliferating cancer cells require large amounts of ferric ion that are present in the active site of RR enzyme for DNA synthesis. Gallium mimics ferric ion and is taken up by the rapidly proliferating cells instead of iron, but is non-functional for DNA synthesis (Higashi et al. 1988; Chitambar et al. 1991; Bernstein 1998). Hence the cells cannot proliferate and die by apoptosis (Chitambar et al. 2007). Clinically gallium is used in its intravenous form as gallium nitrate or its orally bioavailable form gallium maltonate. Both of these agents have demonstrated activities for a wide variety of cancers in clinical setting.

Gallium nitrate was approved by FDA in 1991 for cancer-related hypercalcemia (Krakoff 1991). The results of the phase I and II studies were summarized in Table 3. Several phase II studies were carried out with gallium nitrate for the treatment of breast cancer (Fabian et al. 1982; Jabboury et al. 1989), advanced hypernephroma (Schwartz and Yagoda 1984), malignant melanoma (Casper et al. 1985), lymphoproliferative disorder (Keller et al. 1986), ovarian carcinoma (Malfetano et al. 1991a), squamous cell carcinoma of cervix (Malfetano et al. 1991b), small cell lung cancer (Baselga et al. 1993), colorectal cancer (Canfield

Table 3 Gallium nitrate clinical trials

Drug name	Trial design	Indication	Phase	Outcomes	Dose limiting toxicity (grade 3 or 4)	References
Gallium nitrate	Single agent	Breast cancer	II	No OR	Lymphopenia	Jabboury et al. (1989)
	Single agent	Advanced hyper-nephroma	II	No OR	Nephrotoxicity	Schwartz and Yagoda (1984)
	Single agent	Malignant melanoma	II	PR: 1/31 RR: 3.22%	Not reported	Casper et al. (1985)
	Single agent	Lymphoproliferative disorder	II	PFS: 3.3 RR: 10%	Gastrointestinal, renal toxicity and anemia	Keller et al. (1986)
	Single agent	Ovarian carcinoma	II	CR: 1/26 PR: 2/26 SD: 6/26 RR: 11.5%	Nausea, vomiting and anemia	Malfetano et al. (1991a)
	Single agent	Squamous cell carcinoma of cervix	II	PR: 2/24 SD: 10/24 RR: 8.33%	Nausea, vomiting and anemia	Malfetano et al. (1991b)
	Single agent	Small cell lung cancer	II	No OR	Nausea	Baselga et al. (1993)
	Single agent	Colorectal cancer	II	No OR	Elevated LDH	Canfield and Lyss (1993)
	Single agent	Nonsquamous cell carcinoma of cervix	II	CR: 2/26 PR: 1/26 SD: 13/26 RR: 30.2% (95% CI)	Nausea, vomiting and anemia	Malfetano et al. (1995)
	Single agent	Androgen independent prostate cancer	II	1/8 patient had PSA decrease of >75%	Anemia, blindness and pulmonary toxicity	Senderowicz et al. (1999)
	Single agent	Non small cell lung cancer	II	PR: 1/21 SD: 4/21 RR: 4.76%	Renal impairment and optic neuritis	Webster et al. (2000)
	Single agent	Bladder cancer	II	CR: 1/26 PR: 6/26 PFS: 4 RR: 27%	Nephrotoxicity	(Crawford et al. 1991)
	Single agent	Urothelial malignancy	II	CR: 1/22 PR: 3/22 PFS: 4 RR: 18.18%	Reversible optic neuropathy	Seidman et al. (1991)
	Combination with paclitaxel and filgastrim	Refractory malignancies	I	CR: 1/40 PR: 1/40 SD: 10/40 RR: 5%	Neutropenia	Sandler et al. (1998)
	Combination with amonafide and teniposide	Non-small cell lung cancer	II	No OR	Sepsis, infection and leucopenia	Chang et al. (1995)
	Combination with vinblastine, ifosamide and filgrastim	Urothelial carcinoma	II	CR: 6/45 PR: 14/45 PFS: 10 RR: 44%	Leucopenia and anemia	Dreicer et al. (1997)
	Combination with vinblastine, ifosamide and filgrastim	Advanced ovarian cancer	II	PR: 5/14 RR: 36%	Leucopenia and anemia	Dreicer et al. (1998)
	Combination with 5-fluorouracil	Advanced urothelial tract tumors	II	PR: 2/17 PFS: 19 RR: 12%	Anemia and mucositis	McCaffrey et al. (1997)

CR complete response, *PR* partial response, *RR* response rate (CR + PR) in %, *SD* stable disease, *OR* objective response, *PFS* median progression-free survival (in months) unless otherwise indicated, *OS* median overall survival (in months), unless otherwise indicated, *TTP* median time to progression (in months), unless otherwise indicated, *PSA* prostate serum antigen

and Lyss 1993), non-squamous cell carcinoma of cervix (Malfetano et al. 1995), androgen independent prostate cancer (Senderowicz et al. 1999), non-small cell lung cancer (Webster et al. 2000), bladder cancer (Crawford et al. 1991) and urothelial malignancy (Seidman et al. 1991). Gallium nitrate was found to be moderately efficacious in the treatment of ovarian carcinoma, non-squamous cell carcinoma of the cervix and androgen independent prostate cancer. It was found to be an active agent in the treatment of advanced bladder cancer and urothelial malignancies with manageable toxicity profile (Malfetano et al. 1991b; Dreicer et al. 1998; Senderowicz et al. 1999). Ocular toxicity was seen in urothelial cancer and hence further trials were not carried out (Seidman et al. 1991). Renal toxicity is another major challenge associated with Gallium nitrate above 750 mg/m^2 i.v. dose (Krakoff et al. 1979). With other types of cancers evaluated above, no objective response was seen and hence further clinical trials were not carried out.

Gallium nitrate was also given in combination with other drugs in clinical trials (Table 3). Phase I dose escalation trial of gallium nitrate with paclitaxel and filgrastim were evaluated for refractory malignancies (Sandler et al. 1998). Even though the complete and partial response for the patients in this trial is low, an optimal phase II dose was recommended and was modified subsequently for outpatient purposes. Phase II trial of gallium nitrate with amonafide and teniposide in metastatic non-small cell lung cancer (Chang et al. 1995) were tested and this combination were found to be inactive and the trial did not progress any further. Combination of gallium nitrate with vinblastine, ifosamide and filgrastim (VIG regimen) in patients with urothelial carcinoma (Dreicer et al. 1997) and in advanced ovarian cancer patients resistant to paclitaxel therapy (Dreicer et al. 1998) were evaluated. The response rates of VIG regimen to urothelial carcinoma was moderate with significant cost associated with the hospitalization and hence further trials were not carried out. In ovarian cancer patients who were heavily pretreated before introducing VIG regimen, the response rates were 36% with manageable toxicity and further evaluation of the regimen was warranted. Phase II study of gallium nitrate with 5-fluorouracil in the treatment of advanced urothelial tract tumors (McCaffrey et al. 1997), were compared with methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) regimen. The gallium nitrate/5-FU combination was found to be ineffective and was not investigated further. Overall, it appears that gallium nitrate is more effective as a monotherapy, whereas the combination therapy showed mixed results.

Gallium maltolate is an orally bioavailable form of gallium nitrate that has been developed as possible alternative to gallium nitrate, and is not associated with renal toxicity. Gallium maltolate was found to induce apoptosis and

was active against gallium nitrate-resistant lymphoma cells (Chitambar et al. 2007). Recently, gallium maltolate has been tried in a patient with hepatocellular carcinoma, resistant to sorafenib in phase I study. After 4 weeks of treatment, the patient showed reduced pain, improved mobility and increased quality of life (Chua et al. 2006; Bernstein et al. 2011). Gallium maltolate have also been explored in phase II studies for hormone refractory prostate cancer and various refractory malignancies (http://www.clinicaltrials.gov). Gallium maltolate was also shown to act synergistically with bortezomib to increase its apoptosis activity in lymphoma cells by inhibiting the proteasome (Chitambar and Purpi 2010). This novel finding shows promise and further clinical trials with gallium maltolate as combination therapy is warranted.

Hydroxyurea

Hydroxyurea was one of the first agents developed for the treatment of cancer in 1960's. It acts by scavenging the tyrosine radical thereby inhibiting RR2. Hydroxyurea have been evaluated in several clinical trials either as a single agent or in combination. Hydroxyurea has been evaluated as a single agent in phase I studies (Thurman et al. 1963; Bolton et al. 1964; Griffith 1964) and in phase II studies for the carcinoma of the lung (Bickers 1964), multiple myeloma and lymphoma (Davis 1964), urologic and gynecologic neoplasms (Howe and Samuels 1964), breast cancer (Sears 1964), leukemia (Shullenberger 1964), malignant melanoma (Lerner et al. 1970), and in phase III studies for malignant gliomas (Levin et al. 1979). Hydroxyurea has also been tried as a combination agent with a variety of drugs, in phase I studies for the treatment of cancer of head and neck (Beitler et al. 1998; Brockstein et al. 1998), refractory breast or lung cancer (Raschko et al. 1994), gastrointestinal cancer (Bhalla et al. 1991), leukemia (Lomen et al. 1980; Ratain et al. 1988), advanced malignancies (Wadler et al. 1996) and cervical cancer (Stehman et al. 1997). In phase II studies it has been tried as a combination therapy for chronic myelogenous leukemia (Anger et al. 1989; Archimbaud et al. 1989; Lazzarino et al. 1991), myeloproliferative disease (Litam et al. 1994), pancreatic and gastric tumors (Wadler et al. 2002; Kaubisch et al. 2004), hepatocellular carcinoma (Gebbia et al. 1999), non-small cell lung cancer (Axelson et al. 1987), cervical carcinoma (Stehman et al. 1997), malignant melanoma (Amato et al. 1987; Philip et al. 1994), head and neck carcinoma (Dodion et al. 1986; Vokes et al. 1989; Rosen et al. 2003), malignant gliomas (Levin et al. 1986), colorectal carcinoma (O'Byrne et al. 1999), tumor of the uterus (Currie et al. 1996) and progressive meningiomas (Mazza et al. 2016). Phase III trials were conducted with combination drugs for the treatment of chronic myeloid leukemia (Hehlmann

et al. 2003), malignant gliomas (Levin et al. 1985), renal carcinoma (Stolbach et al. 1981), glioblastoma multiforme (Dresemann et al. 2010) and colorectal cancer (Engstrom et al. 1982). It has been approved for use by FDA in myeloproliferative disorders (Harrison et al. 2005) and sickle cell disease (Charache et al. 1995).

Recently from 2007 onwards hydroxyurea is used more as a combination therapy, rather than a single agent. The results of the trials are summarized in Table 4. The results of phase I studies indicate that the combination with *ara-C* was tolerable and efficacious and shows synergism with *ara-C* (Dubowy et al. 2008). Combination with bevacizumab, fluorouracil and radiation, indicate that the neutropenia observed was due to bevacizumab, but the combination regimen is well tolerated (Seiwert et al. 2008). When valatinib was added to the combination of hydroxyurea and imatinib, the regimen was well-tolerated for malignant glioma patients with a response rate of 24% (Reardon et al. 2009). Phase II studies of hydroxyurea in combination with imatinib for heavily pretreated grade III malignant glioma patients, showed that the combination therapy is well-tolerated and warrants further investigation (Desjardins et al. 2007), whereas the combination therapy in the case of progressive meningiomas remain a challenge with adverse events such as grade 3 neutropenia, headache and vomiting (Mazza et al. 2016). As a monotherapy, both the drugs did not show any individual activity against malignant gliomas (Geyer et al. 1994). Cisplatin when combined with hydroxyurea and *ara-C* did not improve the survival rates in glioblastoma multiforme group as per southwest oncology group. Hematological toxicity significantly increased and further evaluation of this regimen is not warranted (Swinnen et al. 2008). Phase II trial of cetuximab when incorporated along with radiation therapy, 5-fluorouracil and hydroxyurea showed an overall survival rate of 86% and disease free survival rate of 69%, respectively, for 2-year period. The combination was efficacious, well-tolerated and promising therapy for squamous cell carcinoma of head and neck (Kao et al. 2011). However, when bevacizumab was added to a combination of 5-fluorouracil, Hydroxyurea and radiation therapy for intermediate stage T4 head and neck cancers higher response rates were observed, but the study was terminated because of locoregional progression (Salama et al. 2011). Hence, it was recommended to limit addition of bevacizumab in future trials. Overall it appears that the combination therapy is well-tolerated with hydroxyurea in both the phase I and phase II studies.

Open label phase III trial of hydroxyurea in combination with imatinib were tried in recurrent glioblastoma multiforme (GBM) patients who were pretreated with surgery, irradiation therapy or first line chemotherapy with temozolamide (Dresemann et al. 2010). This combination treatment was compared with hydroxyurea monotherapy.

The combination therapy was found to be as efficacious as hydroxyurea monotherapy with a lower response rate of 25% and 6 month progression free survival rate of 5% in combination arm. Grade 3/4 thrombocytopenia and leucopenia were the commonly observed AEs. Overall, the combination is not recommended in GBM relapsing patients. PDGFRa protein expression and phosphorylation status was thought to have a prognostic role in recurrent glioblastomas in these combination therapy patients (Paulsson et al. 2011).

There are also other RR2 inhibitors like nitric oxide, alkoxy phenols, desferrioxamine and PIH. The clinical activities of these agents have not been demonstrated which precludes further discussion.

Current RR1 inhibitors in clinical trials

These inhibitors cause inactivation of protein RR1 by inhibiting the active site or allosteric modulation as well as through regulating gene expression.

GTI-2501

GTI-2501 is a 20-mer oligonucleotide complimentary to the coding region of mRNA of R1, the largest subunit of RR. In vitro and in vivo studies have shown that GTI-2501 decrease the mRNA and protein levels of RR1 in a variety of tumors and have shown tumor regression in animals and two human cancer models (Lee et al. 2006).

Phase I studies of GTI-2501 for patients with solid tumors demonstrated that the compound was safe to use therapeutically (Tu and Tu 2001). Phase I/II studies of GTI-2501 in combination with docetaxel were carried out to define the optimum phase II dose in men with metastatic hormone refractory prostate cancer (Ko et al. 2006). In 13 evaluable patients, the highest dose of GTI-2501 was well-tolerated and the DLT of grade 4 neutropenia observed with one patient was attributed to docetaxel. The combination therapy was further recommended for phase II.

Motexafin gadolinium

Motexafin gadolinium is an inhibitor of both RR and thioredoxin reductase, with a novel mechanism of action. Motexafin gadolinium is an MRI detectable drug that concentrates in cancer cells, induces redox stress and triggers apoptosis in a broad range of tumor cells (Evens 2004; Evens et al. 2005; Zahedi Avval et al. 2009). Motexafin gadolinium has been evaluated in several clinical trials.

The phase I and II clinical trials of motexafin gadolinium is summarized in Table 5. When motexafin gadolinium was administered as a single agent concurrent with radiotherapy

in pancreatic cancer patients in phase I dose escalation studies, the patient did not show any objective response to therapy and 2.9 mg/kg was the recommended phase II dose. It was suggested that the patient's tolerance to treatment may be modified with changing the schedule of radiotherapy and antiemetic prophylaxis (Ramanathan et al. 2006). When evaluated in glioblastoma multiforme patients in phase I studies, the median survival was 16.1 months with motexafin treatment, compared with 11.8 month survival for radiation-treated patients. The dose-limiting toxicities were reversible transaminase elevation and allergic skin

rash in some patients. Nevertheless, motexafin gadolinium was recommended for phase II trials with concurrent radiotherapy and adjuvant temozolomide (Ford et al. 2007). When treated for childhood pontine glioma in phase I studies, the median survival time was 313 days and over half of the patients (out of 44) demonstrated motexafin uptake in day 30. Further phase II studies with motexafin gadolinium were recommended (Bradley et al. 2008).

Phase II studies of motexafin in brain metastasis showed a high response rate of 72%. Hepatotoxicity was the major observed dose limiting toxicity (Carde et al. 2001). The

Table 4 Hydroxyurea clinical trials

Drug name	Trial design	Indication	Phase	Outcomes	Dose limiting toxicity (grade 3 or 4)	References
Hydroxyurea	Combination with cytosine arabinoside (*ara-C*)	Childhood acute leukemia	I	CR: 6/33 PR: 5/33 RR: 33%	Cytopenia	Dubowy et al. (2008)
	Combination with bevacizumab fluorouracil and radiation	Head and neck cancer	I	CR: 18/26 PR: 4/26 SD: 1/26 PFS: 10.3 OS: 10.7 RR: 84.6%	Neutropenia	Seiwert et al. (2008)
	Combination with valatinib and imatinib	Malignant glioma	I	PR: 9/37 SD: 18/37 OS: 11 PFS: 2.7 RR: 24%	Thrombocytopenia	Reardon et al. (2009)
	Combination with imatinib	Grade III malignant glioma	II	PR: 4/39 SD: 13/33 OS: 33 weeks PFS: 11 weeks RR: 10%	Hematologic	Desjardins et al. (2007)
	Combination with *ara-C* and cisplatin	Glioblastoma multiforme	II	PR: 1/51 SD: 13/51 OS: 5 PFS: 2 RR: 2%	Neutropenia	Swinnen et al. (2008)
	Combination with 5-fluorouracil, radiation and cetuximab	Advanced squamous cell carcinoma of head and neck	II	Overall survival rate: 86% Disease free survival rate: 69%	Mucositis	Kao et al. (2011)
	Combination with 5-fluorouracil, radiation and bevacizumab	Intermediate stage T4 carcinoma of head and neck	II	CR: 12/14 Overall survival rate: 58% Progression free survival rate: 59% RR: 86%	Mucositis	Salama et al. (2011)
	Combination with imatinib	Glioblastoma multiforme	III	PFS: 6 Progression free survival rate: 5% Overall survival rate: 40% RR: 25%	Thrombocytopenia	Dresemann et al. (2010)

CR complete response, *PR* partial response, *RR* response rate (CR + PR) in %, *SD* stable disease, *OR* objective response, *PFS* median progression-free survival (in months) unless otherwise indicated, *OS* median overall survival (in months), unless otherwise indicated, *TTP* median time to progression (in months), unless otherwise indicated

treatment was found to be efficacious and further Phase III trials were carried out. Similar observations with single agent were observed by Mehta et al. (2002). Motexafin was also evaluated in renal cell carcinoma patients in phase II studies. Since no complete or partial response is observed, further evaluation of it as single agent is not recommended (Amato et al. 2008). Similarly no complete or partial response was observed when motexafin was evaluated in phase II studies for refractory chronic lymphatic leukemia, further dose optimization for this therapy were suggested to arrive at meaningful clinical response (Lin et al. 2009).

Phase III studies of motexafin gadolinium were evaluated in non-small cell lung cancer patients with brain metastasis along with whole brain radiotherapy. Motexafin increased the time to progression from 10 to 15 months and the interval to neurocognitive progression (Mehta et al. 2009). A phase III study also demonstrated that motexafin may improve memory and executive function and prolong time to neurocognitive and neurologic progression in patients with brain metastases from lung cancer (Meyers et al. 2004).

Motexafin gadolinium has also been tried as a combination therapy. In a phase I study combining docetaxel, cisplatin and radiotherapy for treatment of non-small cell lung cancer, it was observed that the regimen was tolerable and efficacious and was recommended for phase II studies (William et al. 2007). When combined with [(90) Y]Ibritumomab tiuxetan and concurrent radiotherapy for the treatment of non-Hodgkin's lymphoma, the response rate was high at 57%. Most of the patients achieved complete response. Especially, in the case of rituximab refractory patients, the response rate increased to 86% with a median progression-free survival (PFS) of 14 months. The combination of motexafin with radio immunotherapy was efficacious and well-tolerated with minimal side effects and this therapy could be very useful for rituximab refractory patients (Evens et al. 2009). A phase I study combining doxorubicin and concurrent radiotherapy with motexafin did not show any complete or partial response. A phase 1 study of motexafin with temozolomide and radiation therapy in newly diagnosed supratentorial glioblastoma multiforme did not lead to improvement in median overall survival compared to historical control (Brachman et al. 2015). Based on the results of various clinical trials further combination therapy of motexafin gadolinium with other RR inhibitors such as gemcitabine was recommended (Traynor et al. 2011).

Phase II combination study of motexafin with premetrexed and concurrent radiotherapy in non-small cell lung cancer showed that the treatment was well-tolerated with toxicity profile similar to premetrexed alone. However, the study did not achieve its 6 month PFS endpoint of 40% and the overall response rate, median progression free survival and median overall survival did not seem to be different than premetrexed alone when used as a single agent. Hence, development of this combination was not recommended (Edelman et al. 2011).

These results suggest motexafin gadolinium shows promising activity as a monotherapy and in some combination therapies. Since the drug is active in phase III, further development of this agent in various cancers are promising.

Gemcitabine

Gemcitabine is a nucleoside analog in which the 2′ carbon of deoxy cytidine is replaced by fluorine atom. Deoxycytidine kinase metabolizes gemcitabine to its monophosphate and subsequently to diphosphate and triphosphate by other intracellular kinases. The diphosphate inhibits RR leading to loss of catalytic activity (Baker et al. 1991), thereby the ribonucleotides required for DNA replication and repair are not produced, leading to apoptosis. Alternately, the gemcitabine triphosphate formed competes with the cytidine triphosphate for incorporation into replicating DNA. Once gemcitabine triphosphate is incorporated, only one more nucleotide could be attached to this faulty nucleotide, resulting in apoptosis (Huang et al. 1991). Gemcitabine has been approved by FDA for the treatment of pancreatic cancer (Storniolo et al. 1999). Gemcitabine is also approved as a combination therapy by the FDA for the treatment of metastatic breast cancer with paclitaxel (Roy et al. 2009) and for the treatment of non-small cell lung cancer (Scagliotti et al. 2008) in combination with cisplatin. It has also been approved by European Medicines Agency in combination with cisplatin for the treatment of bladder cancer (Vallo et al. 2015). Gemcitabine and carboplatin have also been approved for ovarian cancer (Pfisterer et al. 2005). Currently several clinical trials are underway for gemcitabine at phase I, II and III stages either as a single agent or as a combination. Some of the clinical trials associated with gemcitabine from year 2007 onwards are listed in Table 6 and most of the clinical trials with gemcitabine are usually in combination with two or three agents.

Phase III studies of intravesical infusion of gemcitabine and mitomycin as single agents were compared in patients with recurrent superficial bladder cancer. The results of the trial demonstrate that 72% of patients were recurrent free in gemcitabine arm as compared to 61% in the mitomycin arm. The adverse effects of hematuria and cystitis were also lower in gemcitabine arm as compared to mitomycin arm. Hence gemcitabine appears as a logical treatment for bladder cancer (Addeo et al. 2010). When gemcitabine versus pegylated liposomal doxorubicin (current standard of care) were compared in 195 patients with platinum resistant ovarian cancer, it was found that the median PFS in gemcitabine group is 3.6 months as compared to pegylated

Table 5 Motexafin gadolinium clinical trials

Drug name	Trial design	Indication	Phase	Outcomes	Dose limiting toxicity (grade 3 or 4)	References
Motexafin gadolinium	Single agent with concurrent radiotherapy	Pancreatic cancer	I	No OR PFS: 6	Nausea and vomiting, skin toxicity	Ramanathan et al. (2006)
	Single agent with concurrent radiotherapy	Glioblastoma multiforme	I	PFS: 16.1	Reversible transaminase elevation	Ford et al. (2007)
	Single agent with concurrent radiotherapy	Pontine glioma in children	I	PFS: 10.3	Hypertension and serum transaminase elevation	Bradley et al. (2008)
	Single agent with concurrent radiotherapy	Brain metastasis	II	PR: 13/18 SD: 4/18 PFS: 4.7 RR: 72%	Hepatotoxicity	Carde et al. (2001)
	Single agent with concurrent radiotherapy	Renal cell carcinoma	II	SD: 8/20 OS: 10.1 PFS: 2.7	Hypophosphatemia	Amato et al. (2008)
	Single agent with concurrent radiotherapy	chronic lymphatic leukemia	II	No CR or PR	Anemia, hypophosphatemia	Lin et al. (2009)
	Single agent with concurrent	Brain Metastasis	III	PFS: 5.1	Liver function abnormalities	Mehta et al. (2009)
	Combination with docetaxel, cisplatin and concurrent radiotherapy	Non-small cell lung cancer	I	PR: 2/21 SD: 12/21 OS: 7.3 PFS: 3.5 RR: 10%	Febrile neutropenia, hypertension	William et al. (2007)
	Combination with [(90)Y]Ibritumomab tiuxetan and concurrent radiotherapy	Refractory non-Hodgkin's lymphoma	I	CR: 12/28 OS: 5 PFS: 10 RR: 57%	Hematologic	Evens et al. (2009)
	Combination with doxorubicin and concurrent radiotherapy	Advanced solid tumors	I	SD: 6/15 MP: 49 days	Hypertension, pneumonia, bacteremia	Traynor et al. (2011)
	Combination with temozolomide and radiation therapy	Gliablastoma multiforme	I	PFS: 7.6 OS: 15.6	Neurologic	Brachman et al. (2015)
	Combination with Premetrexed and concurrent radiotherapy	Non-small cell lung cancer	II	PR: 5/62 SD: 35/62 OS: 8.1 PFS: 2.6 RR: 8%	Neutropenia	Edelman et al. (2011)

CR complete response, *PR* partial response, *RR* response rate (CR + PR) in %, *SD* stable disease, *OR* objective response, *PFS* median progression-free survival (in months) unless otherwise indicated, *OS* median overall survival (in months), unless otherwise indicated, *TTP* median time to progression (in months), unless otherwise indicated

doxorubicin group (3.1 months). However, the overall survival and overall response rate in pegylated doxorubicin group is slightly higher at 13.5 months (compared to 12.7 months in Gemcitabine group) and 8.3% (compared to 6.1% in gemcitabine group). None of these efficacy values showed statistically significant differences. However, the pegylated liposomal doxorubicin group experienced significantly more toxicity such as hand and foot syndrome and mucositis. Based on the toxicity profile, gemcitabine is suggested as an alternative to doxorubicin therapy (Mutch et al. 2007).

In a phase I trial of gemcitabine with erlotinib and radiation therapy for non-operable pancreatic adenocarcinoma patients, it was found that the combination was well-tolerated with a median overall survival of 18.7 months and warrants further investigation (Duffy et al. 2008). When gemcitabine was combined with oxaliplatin and capecitabine for upper gastrointestinal malignancies, the treatment was found to be efficacious with manageable toxicity profile. For patients with pancreatic cancer a median survival time of 13.4 months was observed with this regimen compared to 3.3 months for patients who progressed (Tan et al.

2008). This trial will be conducted further at phase II level. Combination therapy with docetaxel for chemotherapy resistant ovarian cancer showed an overall response rate of 29% with manageable hematological effects and hence this combination is acceptable for phase II studies (Itani et al. 2009). Recent combination Phase I trial with vinflunine for chemo naive non-small cell lung cancer patients demonstrated that the treatment was efficacious with excellent response rates and manageable toxicity that warrants further phase II testing (Tournoux-Facon et al. 2011).

There are several trials (more than 300) of gemcitabine combination therapy in phase II studies. Some of the selected study results are discussed below. Combination study with docetaxel as a first-line therapy for metastatic urothelial carcinoma patients, showed a high response rate with less toxicity as compared to standard cisplatin regimen and hence further large-scale studies were warranted to confirm these observations (Neri et al. 2007). For advanced biliary cancer, gemcitabine was combined with capecitabine and the treatment showed a response rate of 29%, with an overall survival time of greater than one year, which is better than the current treatment (Riechelmann et al. 2007). Phase II study of gemcitabine with oxaliplatin and capecitabine for metastatic pancreatic cancer showed a median overall survival of 11.9 months compared to 9.1 months with gemcitabine alone. Hematologic and non-hematologic toxicities were severe, yet tolerable with combination chemotherapy (Petrioli et al. 2015). Gemcitabine was combined with mitoxantrone and rituximab for the treatment of mantle cell lymphoma. The study achieved a response rate of 46% with dose limiting toxicity of neutropenia and thrombocytopenia that are manageable (Garbo et al. 2009). Further follow-up studies are necessary with the regimen, although combination with bortezomib is emerging as an alternative (Kouroukis et al. 2011). Combination of dacarbazine and gemcitabine were tried in soft tissue sarcoma patients. The results of the phase II studies demonstrate that the combination showed a median progression free survival of 4.2 months (as compared to 2 months for gemcitabine alone) and overall survival of 16.8 months (as compared with 8.2 months for gemcitabine alone). Toxicities such as neutropenia were manageable and this regimen could be an alternative therapy for patients with soft tissue sarcoma (Garcia-Del-Muro et al. 2011). Erlotinib as a single agent yielded disappointing results for treatment of advanced pretreated breast cancer. However, when erlotinib was combined with gemcitabine in a phase II study, overall response rate of 14% were observed with a median progression free survival of 2.8 and 6 months survival rate of 75%, and the treatment was well tolerated (Graham et al. 2005). In a phase II study of metastatic breast cancer HER 2-positive patients, gemcitabine in combination with trastuzumab was well-tolerated

with a median overall survival of 14.7 months and objective response rate of 38%. Grade 4 neutropenia were observed with minority of patients (O'Shaughnessy et al. 2004).

In a phase III study comparing anthracycline pretreated gemcitabine–docetaxel combination with capecitabine–docetaxel patients for advanced breast cancer, the time to treatment failure or disease progression was lower in gemcitabine arm as compared to the docetaxel arm. The progression free survival, overall survival and response rates were similar in both the arms. However, grade 3–4 diarrhoea, mucositis and hand–foot syndrome were significantly higher in capecitabine–docetaxel arm. Based on the toxicity profile gemcitabine–docetaxel regimen is recommended in clinical setting (Chan et al. 2009). In a phase III study in metastatic pancreatic ductal adenocarcinoma patients, combination of Nab-Paclitaxel (albumin bound paclitaxel) with gemcitabine showed superior activity and efficacy compared to gemcitabine alone. The overall response rate for the combination was 36.6%. The median progression free survival and overall survival were also higher for the combination arm. Grade 3 neutropenia, thrombocytopenia and anemia were the only adverse events. No grade 4 adverse events were observed (De Vita et al. 2016). In a phase III study comparing gemcitabine + cisplatin combination versus fluorouracil + cisplatin in patients with recurrent or metastatic nasopharyngeal carcinoma, as a first line chemotherapy, gemcitabine + cisplatin combination outperformed fluorouracil + cisplatin combination in progression free survival, overall survival and proportion of patients receiving objective response. Grade 3 hematological adverse events were observed in gemcitabine + cisplatin arm and these results establish gemcitabine + cisplatin as current first line treatment for metastatic nasopharyngeal carcinoma (Zhang et al. 2016). In a phase III study comparing gemcitabine + cisplatin combination versus cisplatin alone in chemotherapy-naïve patients with metastatic non-small cell lung cancer (NSCLC), higher incidences of grade 4 neutropenia (35.4%) and thrombocytopenia (25.4%) were observed in the combination arm of gemcitabine + cisplatin. However, gemcitabine + cisplatin combination showed an improved overall survival of 9.1 versus 7.1 months with cisplatin, improved response rate of 30.4 versus 11.1% with cisplatin. Hence the gemcitabine + cisplatin combination is recommended as a first line therapy for NSCLC (Sandler et al. 2000).

These are the examples of successful clinical trials with gemcitabine. However, there are other phase III trials where presence of gemcitabine did not demonstrate any additional clinical benefit (du Bois et al. 2010; Halim et al. 2011; Weissman et al. 2011) as a combination therapy. Based on the published clinical trials it appears that gemcitabine is effective both as a monotherapy and as a combination,

Table 6 Gemcitabine clinical trials

Drug name	Trial design	Indication	Phase	Outcomes	Dose limiting toxicity (grade 3 or 4)	References
Gemcitabine	Single agent	Superficial bladder cancer	III	% Free of recurrence: 72%	Hematurea and cystitis	Addeo et al. (2010)
	Single agent	Platinum resistant ovarian cancer	III	OS: 12.7 PFS: 3.6 RR: 6.1%	Constipation, nausea and vomiting	Mutch et al. (2007)
	Combination with erlotinib and radiation	Pancreatic adenocarcinoma	I	PR: 6/17 SD: 9/17 OS: 18.7 TP: 13 RR: 35.2%	Neutropenia and thrombocytopenia	Duffy et al. (2008)
	Combination with oxaliplatin and capecitabine	Advanced upper gastrointestinal malignancies	I	CR: 1/23 PR: 2/23 SD: 9/23 RR: 13%	Dyspnea	Tan et al. (2008)
	Combination with docetaxel	Chemotherapy resistant ovarian cancer	I	CR: 1/32 PR: 6/32 SD: 6/32 PFS: 13 TP: 4.8 RR: 21.9%	Neutropenia	Itani et al. (2009)
	Combination with vinflunine	Non-small cell lung cancer	I	PR: 7/19 SD: 8/19 OS: 13.6 PFS: 4.2 RR: 36.8%	Neutropenia and constipation	Tournoux-Facon et al. (2011)
	Combination with docetaxel	Metastatic urothelial carcinoma	II	CR: 4/32 PR: 13/32 SD: 6/32 OS: 14.8 TTP: 10.2 RR: 53.1%	Neutropenia and thrombocytopenia	Neri et al. (2007)
	Combination with capecitabine	Advanced biliary cancer	II	CR: 3/75 PR: 19/75 SD: 37/75 OS: 12.7 PFS: 6.2 TTP: 10.2 RR: 29%	Neutropenia and thrombocytopenia	Riechelmann et al. (2007)
	Combination with oxaliplatin and capecitabine	Metastatic pancreatic cancer	II	PR: 12/34 SD: 15/34 OS: 11.9 PFS: 6.8 RR: 79.4%	Neutropenia, anemia and thrombocytopenia	Petrioli et al. (2015)
	Combination with mitoxantrone and rituximab	Relapsed or refractory mantle cell lymphoma	II	CR: 3/15 PR: 4/15 SD: 2/15 RR: 46%	Neutropenia and thrombocytopenia	Garbo et al. (2009)
	Combination with dacarbazine	Soft tissue sarcoma	II	SD: 14/29 OS: 16.8 PFS: 4.2 RR: 12%	Granulocytopenia	Garcia-Del-Muro et al. (2011)
	Combination with erlotinib	Advanced breast carcinoma	II	PFS: 2.8 RR: 14%	–	Graham et al. (2005)
	Combination with trastuzumab	Advanced breast cancer	II	OS: 14.7 TTP: 5.8 RR: 38%	Neutropenia	O'Shaughnessy et al. (2004)

Table 6 continued

Drug name	Trial design	Indication	Phase	Outcomes	Dose limiting toxicity (grade 3 or 4)	References
	Combination with docetaxel	Metastatic breast cancer	III	OS: 19.29 PFS: 8.05 TTP: 4.24 RR: 32%	Leucopenia	Chan et al. (2009)
	Combination with nab-paclitaxel	Metastatic pancreatic ductal adenocarcinoma	III	CR: 2/41 PR: 13/41 SD: 14/41 OS: 10 PFS: 6.7 RR: 36.6%	Neutropenia, thrombocytopenia and anemia	Chan et al. (2009)
	Combination with cisplatin	Metastatic nasopharyngeal carcinoma	III	CR: 15/181 PR: 101/181 SD: 46/181 OS: 29.1 PFS: 7 RR: 64%	Leucopenia, neutropenia, thrombocytopenia	Zhang et al. (2016)
	Combination with cisplatin	Non-small cell lung cancer	III	OS: 9.1 RR: 30.4%	Neutropenia, thrombocytopenia	Sandler et al. (2000)

CR complete response, *PR* partial response, *RR* response rate (CR + PR) in %, *SD* stable disease, *OR* objective response, *PFS* median progression-free survival (in months) unless otherwise indicated, *OS* median overall survival (in months), unless otherwise indicated, *TTP* median time to progression (in months), unless otherwise indicated

although in most of the clinical studies it is used more as a combination therapy.

Tezacitabine

Tezacitabine is a deoxycytidine analog which undergoes intracellular phosphorylation to form the diphosphate which irreversibly inhibits the RR and chain terminates DNA (Kanazawa et al. 1998). Tezacitabine inhibits both RR1 and RR2. Tezacitabine also is more resistant to cytidine deaminase enzymes compared to gemcitabine, hence has potential use in tumors where cytidine deaminase enzymes are over expressed (Skierski et al. 1999).

Tezacitabine has been evaluated in both phase I and phase II studies. Phase I dose finding studies for tezacitabine administered twice a week, found the maximum tolerated dose to be 16 mg/m^2 (Burtness et al. 2000). In a phase I study of tezacitabine for refractory solid tumor malignancies, one patient demonstrated a partial response and seven patients exhibited stable disease out of 70 evaluable patients. Grade 3 or 4 neutropenia is the dose-limiting toxicity. Overall, tezacitabine was well-tolerated and was further recommended for phase II trials (Rodriguez et al. 2002). Among the combination studies of tezacitabine, a phase I study of tezacitabine with cisplatin was evaluated in patients, for the treatment of advanced cancer. The study results demonstrated 2 partial responses and 4 stable diseases in 18 evaluable patients with gastrointestinal tumors. Thrombocytopenia and neutropenia were the dose-limiting toxicities and the study was further recommended for phase II evaluation at a dose of 500 mg/m^2 of tezacitabine and 50 mg/m^2 of cisplatin (Flaherty et al. 2003). A combination study of 5-fluorouracil for advanced solid tumors showed that 4 patients out of 20 evaluable patients showed a partial response and 7 out of 20 showed stable disease. Neutropenia was the dose-limiting toxicity. The regimen was well-tolerated in patients with esophageal and other gastrointestinal carcinomas (Bendell et al. 2005).

Phase II study of tezacitabine in patients with advanced colorectal cancer demonstrate that the overall response rate was 11% with 1 complete response and 4 partial response out of 45 evaluable patients. 7% of the patients developed febrile neutropenia as dose-limiting toxicity (Brooks et al. 2003). Phase II studies of tezacitabine for treatment of gastroesophageal cancer, non-small cell lung cancer were terminated (Seley 2000). Phase II studies of combination therapy of tezacitabine with oxaliplatin were also terminated. The lack of efficacy was the reason for the termination of phase II trial for gastroesophageal cancer as disclosed by the company. Overall, tezacitabine showed promise as a single agent and in combination for phase I studies, but did not proceed beyond the phase II studies.

Cladribine and fludarabine

Cladribine and fludarabine are deoxy adenosine analogs that require intracellular phosphorylation for their cytotoxic effect. In proliferating cells cladribine inhibits RR enzyme,

as well as DNA polymerase (Griffig et al. 1989) and adenosine deaminase (Jehn et al. 1993) thereby inhibiting DNA synthesis (Fidias et al. 1996). Fludarabine in its triphosphate form is a potent inhibitor of RR (Brockman et al. 1977; Parker et al. 1991; Gandhi and Plunkett 2002), DNA polymerase (Huang et al. 1990), DNA ligase (Yang et al. 1992) and DNA primase (Catapano et al. 1991). Fludarabine depletes the dNTP pools in tumor cells, thereby exerting its RR inhibition effect. Several clinical trials were conducted with both cladribine and fludarabine.

Cladribine is the drug of choice for hairy cell leukemia (Piro et al. 1990; Saven and Piro 1992). Cladribine is also effective in chronic lymphocytic leukemia (Juliusson et al. 1992; Saven and Piro 1993). Some of the clinical trial results of cladribine are summarized below in Table 7. Phase I trial of cladribine for patients with lymphoid malignancies showed a response rate of 40% with manageable toxicities. Further phase II studies are in progress based on the results (Tobinai et al. 1997).

Cladribine was also evaluated in phase II studies for B cell lymphoma of mucosa associated lymphoid tissue (MALT). The overall response rate was 100% with complete response occurring in 86% of the patients. The dose-limiting toxicity was leucopenia. The treatment was highly efficacious and could be safely administered on outpatient basis (Jager et al. 2002). When cladribine was evaluated in a phase II study for Non-Hodgkin's lymphoma, the treatment was found to be efficacious with a response rate of 58.1%. However, prolonged myelosuppression and development of myelodysplastic syndrome must be monitored carefully in clinical trials (Ogura et al. 2004).

Cladribine were tried in combination with gemcitabine in phase II studies for hematologic malignancies. Several responses were observed in patients with Hodgkin's disease. The treatment was considered to be efficacious with acceptable toxicity profile and further Phase II trials were recommended (Odenike et al. 2004). Phase II studies were also carried out by adding imatinib to a combination of cytarabine (ara-C), granulocyte colony stimulating factor (G-CSF) in pretreated refractory acute myeloid leukemia patients. The results show that overall response rate was 43.8% and an overall survival of 6 months. The toxicities observed were skin rash and nausea. The treatment was found to be efficacious and larger Phase II trials were planned (Walker et al. 2008).

A phase III trial of cladribine with daunorubicin and ara-C for acute myeloid leukemia demonstrates that addition of cladribine increases antileukemic potency of daunorubicin and ara-C regimen, resulting in higher complete response rate (63.5%) after one induction cycle as compared to daunorubicin and ara-C treatment (47%), with manageable toxicity. Thus, addition of cladribine may improve long-term survival in patients greater than 40 years (Holowiecki

et al. 2004). A phase III study comparing cladribine and cyclophosphamide versus fludarabine with cyclophosphamide for chronic lymphocytic leukemia demonstrated that both the treatment have similar efficacy and thereby considered as safe first line regimen for progressive chronic lymphocytic leukemia (Robak et al. 2010).

Fludarabine is effective in the treatment of chronic lymphocytic leukemia producing higher response rates than the alkylating agents such as chlorambucil (Rai et al. 2000). It is also used in the treatment of acute myelogenous leukemia and hematological malignancies (Keating et al. 1994a, b; Wright et al. 1994; Montefusco et al. 2001; Sanz et al. 2010). Fludarabine is also known to act synergistically with other agents such as ara-C in the treatment of chronic lymphocytic leukemia (Gandhi et al. 1994). Currently in most of the clinical trials fludarabine is used as a combination therapy. Some of the clinical trials of fludarabine are discussed in Table 8.

A phase III trial of fludarabine as a single agent was compared against cyclophosphamide, vincristine and prednisone (CVP) in previously untreated low-grade non-Hodgkin's lymphoma. The overall response rate (70%) as well as complete response rate (38.6%) were higher in fludarabine group as compared to CVP group and are statistically significant. There was no statistical difference in overall survival and time to progression. The toxicities were mostly hematological such as granulocytopenia. Overall, fludarabine is active as a single agent in phase III trial and further evaluation of fludarabine combination therapies are warranted (Hagenbeek et al. 2006).

Fludarabine was combined with triapine in a phase I study. The response rate was 20.8% in patients treated with triapine for 4 h followed by fludarabine daily. Especially in patients with myeloproliferative disorder the response ratio was 29%. This combination therapy is active in acute refractory leukemia and warrants further investigations for myeloproliferative disorder (Karp et al. 2008). Based on the hypothesis that bortezomib may potentiate the activity of fludarabine, a combination phase I study of fludarabine, bortezomib and rituximab for relapsed and refractory indolent and mantle cell non-Hodgkin lymphoma was evaluated. The response rate was 45% with a clinical benefit of 71%. The regimen is active with myelosuppression and neuropathy as the dose limiting toxicities. It was further recommended for phase II study with hematopoietic growth factor to minimize myelosuppression caused by rituximab (Barr et al. 2009). A combination therapy of fludarabine with oxaliplatin, ara-C and rituximab was carried out as a phase I study for Richter's syndrome (or) fludarabine refractory chronic lymphocytic leukemia. The response rate was 50% in Richter's syndrome and 33% in fludarabine refractory chronic lymphocytic leukemia. The median response duration was 10 months. The combination

regimen is highly active and warrants further investigation (Tsimberidou et al. 2008).

Phase II studies of fludarabine in combination with rituximab for relapsed indolent B-cell non-Hodgkin lymphoma shows that the therapy is efficacious with high response rates of 76% and long median progression free survival of 19.7 months with manageable toxicity profiles. Hence the therapy is recommended for patients in outpatient setting and further trials as frontline therapy for non-Hodgkin's lymphoma is warranted (Tobinai et al. 2009). Fludarabine was also combined with mitoxantrone and rituximab (FMR) to cause induction followed by radio immunotherapy with 90Y-ibritumomab tiuxetan for untreated intermediate/high risk follicular non-Hodgkin's lymphoma patients. The response rate for the combination therapy was 96% and by the end of treatment 49 of 55 patients achieved complete response. The estimated overall survival for the 3 year period is 100%. This study confirms that radio immunotherapy consolidation could be an important treatment approach for patients with follicular Non-Hodgkin's lymphoma (Zinzani et al. 2011).

Phase III studies of fludarabine in combination with *ara-C* and Idarubicin for the treatment of acute myeloid leukemia in young adults were carried out and compared against Etoposide, *ara-C* and idarubicin treatment. The initial response rate was 75% for fludarabine treated group which increased to 81% after high dose of *ara-C*. The comparable final response in etoposide group is 69%. The probability of overall survival after 4 years in both the arms was similar at 32% and the progression free survival is 31.5% in fludarabine arm as compared to 44% for the etoposide arm. The randomized study confirms the antileukemic activity and low toxicity profile of newly diagnosed acute myeloid leukemia patients (Russo et al. 2005). Fludrabine + cytarabine combination was also more efficacious than fludrabine alone with higher complete response rate (24 versus 7%) and overall response rate (94 vs 83%) compared to fludarabine alone in treatment naïve younger patients with advanced chronic lymphocytic leukemia (Eichhorst et al. 2006). Increased thrombocytopenia and leukocytopenia were observed with this combination.

Cladribine and fludarabine are efficacious both as a single agent and as a combination for cancer therapy. The promising results seen in the phase III trial merit further development of these agents for the treatment of various types of cancers.

Caracemide

Caracemide is known to specifically inhibit RR1 in *E. coli* irreversibly by forming covalent bonds with the cysteine or serine residue at the active site of the enzyme (Larsen et al. 1992). It is also known to inhibit RR1 of tumor cells (Moore and Loo 1984). Caracemide has been evaluated in several clinical trials as antitumor agent in phase I studies (Pazdur et al. 1987; Raber et al. 1987), as well for the treatment of non-small cell lung cancer (Belani et al. 1987) and bronchiogenic carcinoma (Lad et al. 1992) in phase II studies. It was also tried as a combination agent with homoharringtonine for advanced colorectal cancer (Witte et al. 1999) and with amonafide and homoharringtonine for the treatment of renal cell carcinoma (Witte et al. 1996). However, most of these clinical trials had severe dose limiting toxicities such as burning pain (Pazdur et al. 1987), renal failure (Witte et al. 1999), respiratory failure and neurologic dysfunction (Witte et al. 1996), thereby preventing the further development and clinical trials of carecemide.

Clofaribine

Clofarabine is a deoxyadenosine analog approved by the FDA for the treatment of relapsed or refractory acute lymphoblastic leukemia (ALL) in children (Lang et al. 2014). Clofarabine combines the favorable properties of both fludarabine and cladribine, but is much more potent in damaging the DNA of cancer cells. Clofarabine triphosphate acts by inhibiting both DNA polymerase, ribosomal reductase and deoxy cytidine kinase (Xie and Plunkett 1996). The downstream effect is the damage of mitochondria of the cell thereby initiating apoptosis (Genini et al. 2000). Clofarabine has been evaluated in number of clinical trials as a monotherapy as well as in combination. The details of the trials are summarized in Table 9.

Several clinical studies were conducted using clofarabine as monotherapy. In a phase I study of clofarabine for solid hematologic malignancies in thirty-two patients with acute leukemia, the response rate was 16% with reversible hepatotoxicity being the dose limiting toxicity. For solid tumors the dose limiting toxicity is myelosuppression. The treatment is reported active for acute leukemia (Kantarjian et al. 2003). When oral clofarabine was evaluated for relapsed/refractory non-Hodgkin lymphomas in 30 patients in a phase I study, the tumor volume was reduced in 70% of patients with an overall response rate of 47% and complete remission of 27%. Grade 4 neutropenia and thrombocytopenia were the common adverse events observed and further investigation in phase II trials was warranted for this disease population (Abramson et al. 2013). A phase II study of clofarabine in heavily pretreated pediatric patients with relapsed acute lymphoblastic leukemia (ALL) was evaluated. The response rate is 30% with febrile neutropenia being the dose-limiting toxicity. Clofarabine is not associated with neurotoxicity as observed with other nucleoside analogs. Overall, the treatment is efficacious with manageable toxicity profile and further studies are ongoing (Jeha

Table 7 Cladribine clinical trials

Drug name	Trial design	Indication	Phase	Outcomes	Dose limiting toxicity (grade 3 or 4)	References
Cladribine	Single agent	Lymphoid malignancies	I	CR: 1/10 PR: 3/10 RR: 40%	Hypoxemia, Neutropenia and Thrombocytopenia	Tobinai et al. (1997)
	Single agent	B-cell lymphoma of mucosa associated lymphoid tissue	II	CR: 21/25 PR: 4/25 RR: 100%	Leucopenia	Jager et al. (2002)
	Single agent	Non-Hodgkin's lymphoma	II	CR: 6/43 PR: 19/43 PFS: 7.8 RR: 58.1%	Cytopenia	Ogura et al. (2004)
	Combination with gemcitabine	Hematologic malignancies	I	CR: 2/45 PR: 3/45 RR: 11.11%	Skin rash	Odenike et al. (2004)
	Combination with cytarabine (ara-C), G-CSF and imatinib	Refractory acute myeloid leukemia	I	CR: 7/16 OS: 6 RR: 43.8%	Rash, nausea	Walker et al. (2008)
	Combination with daunorubicin and cytarabine	Acute myeloid leukemia	III	CR: 127/200 RR: 72%	Granulocytopenia and thrombocytopenia	Holowiecki et al. (2004)
	Combination with cyclophosphamide	Chronic lymphocytic leukemia	III	CR: 90/192 PFS: 2.34 years RR: 88%	Infections, cytopenia	Robak et al. (2010)

CR complete response, *PR* partial response, *RR* response rate (CR + PR) in %, *SD* stable disease, *OR* objective response, *PFS* median progression-free survival (in months) unless otherwise indicated, *OS* median overall survival (in months), unless otherwise indicated, *TTP* median time to progression (in months), unless otherwise indicated

et al. 2006). Clofarabine was also evaluated in heavily pretreated pediatric population with relapsed acute myeloid leukemia (AML) in a phase II study. The treatment was active and well-tolerated with a response rate of 26% and manageable dose-limiting toxicities (Jeha et al. 2009). In older patients with untreated AML, clofarabine was found to be active with overall response rate of 46% in a phase II study (Kantarjian et al. 2010). When low dose of clofarabine was administered to elderly myelodysplastic syndrome patients resistant to 5-azacytidine, 44% of patients showed a response but with severe pancytopenia as dose-limiting toxicity in all the patients. Further evaluation of this study in large population is warranted (Lim et al. 2010).

Clofarabine can be combined with other drugs as a part of combination therapy to synergistically increase the activity of other drug or potentiate its action. In a phase I combination study with cyclophosphamide for the treatment of acute myeloid leukemia in adults, 2 out of 6 patients achieved complete response at dose level 1 (20 mg/m^2 clofarabine + cyclophosphamide) with an overall response rate of 50% and 3 out of 12 patients achieved complete response and 1 partial response at dose level 0 (10 mg/m^2 clofarabine + cyclophosphamide) with an overall response rate of 33%. The dose limiting toxicity is prolonged bone marrow aplasia. The results suggest that combination

therapy is useful (Karp et al. 2007). Combination of clofarabine with busulfan followed by allogenic stem cell transplantation for acute leukemia showed an overall response rate of 86%. All the patients achieved complete response. The 1 year event-free survival was 53% and overall survival is 60%. The patients demonstrated good tolerability and promising results and this study drug combination was further recommended for phase II trials (Farag et al. 2011). Clofarabine was combined with etoposide and cyclophosphamide for refractory acute leukemia pediatric patients. The overall response rate is 64% (55% for acute lymphoblastic leukemia and 100% acute myelogenous leukemia). Unexpected hepatotoxicity at phase II, led to modification of the trial and is in progress currently (Hijiya et al. 2009). Cytarabine (*ara-C*) was combined with clofarabine for treatment of acute lymphocytic leukemia in adult patients. The response rate was low at 17%, with increased expression of connective tissue growth factor (CTGF) that could explain the low response rate and decreased overall survival (Advani et al. 2010). This regimen was not pursued further. The same combination of *ara-C* and clofarabine were evaluated in refractory acute lymphoblastic leukemia and adult patients. The overall response rate was 53% and median disease-free survival interval was 9.5 months. Half of the patients that showed complete remission were able to

Table 8 Fludarabine clinical trials

Drug name	Trial design	Indication	Phase	Outcomes	Dose limiting toxicity (grade 3 or 4)	References
Fludarabine	Single agent	Low grade malignant non-Hodgkin lymphoma	III	CR: 75/194 PR: 61/194 RR: 70%	Granulocytopenia	Hagenbeek et al. (2006)
	Combination with triapine	Refractory acute leukemia and myeloproliferative disorder	I	CR: 2/24 PR: 3/24 RR: 20.8%	Fever and metabolic acidosis	Karp et al. (2008)
	Combination with bortezomib and rituximab	Non-Hodgkin lymphoma	I	CR: 3/24 PR: 8/24 SD: 6/24 RR: 45%	Myelosuppression and neuropathy	Barr et al. (2009)
	Combination with oxaliplatin, *ara-C* and rituximab	Richter's syndrome	I	CR: 4/20 PR: 6/20 RR: 50%	Hematologic	Tsimberidou et al. (2008)
	Combination with rituximab	Relapsed indolent B-cell non-Hodgkin lymphoma	II	CR: 28/41 PR: 6/41 RR: 76% PFS: 19.7	Neutropenia	Tobinai et al. (2009)
	Combination with rituximab, mitoxantrone followed by 90Y-ibritumomab tiuxetan	Intermediate/high risk follicular lymphoma	II	CR: 38/55 PR: 15/55 RR: 96%	Neutropenia	Zinzani et al. (2011)
	Combination with *ara-C* and idarubicin	Acute myeloid leukemia	III	CR: 42/57 RR: 74%	Intestinal toxicity	Russo et al. (2005)
	Combination with cyclophosphamide	Chronic lymphocytic leukemia	III	CR: 27/164 PR: 128/164 PFS: 48 RR: 94%	Thrombocytopenia and leukocytopenia	Eichhorst et al. (2006)

CR complete response, *PR* partial response, *RR* response rate (CR + PR) in %, *SD* stable disease, *OR* objective response, *PFS* median progression-free survival (in months) unless otherwise indicated, *OS* median overall survival (in months), unless otherwise indicated, *TTP* median time to progression (in months), unless otherwise indicated

proceed to curative hematopoietic stem cell transplantation. The treatment was found to be active in these set of patients (Agura et al. 2011). Clofarabine was also evaluated in combination with etoposide and mitoxantrone in patients with refractory or relapsed acute leukemia in a Phase I/II studies with an overall response rate of 36% (Abbi et al. 2015) and shows promise for further evaluation. In a Phase III trial, clofarabine + *ara-C* was compared with placebo + *ara-C* in patients >55 years old with relapsed acute myelogenous leukemia (AML). Combination of Clofarabine + *ara-C* showed improved overall survival, event free survival/progression free survival with grade 3 toxicities of febrile neutropenia, hypokalemia, thrombocytopenia in clofarabine + *ara-C* arm (Faderl et al. 2012).

Overall, clofarabine is active both as a monotherapy and as a combination agent for the treatment of wide variety of cancers. Currently, clofarabine is evaluated in phase III studies along with *ara-C*, decitabine and daunorubicin for acute myeloid leukemia (Foran 2014).

Other RR1 inhibitors like 2′-deoxy-2′-methylidenecytidine (DMDC), cytarabine and ADP-S-HBES-S-dGTP have been replaced by better agents in clinic such as gemcitabine, cladribine and fludarabine, which precludes further discussion of these agents.

Conclusions

Majority of the RR2 inhibitors such as triapine, GTI-2040, didox, gallium nitrate and maltolate have been evaluated in phase II trials (Webster et al. 2000; Nutting et al. 2009; Traynor et al. 2010; Sridhar et al. 2011). Hydroxyurea has been evaluated in phase III studies (Levin et al. 1979) whereas siRNA therapy is currently under evaluation in phase I study (Davis 2009).

Among the RR2 inhibitors evaluated, GTI-2040, siRNA, gallium nitrate and didox were more efficacious as a monotherapy, whereas triapine was found to be more efficacious as combination therapy. Gallium nitrate showed mixed results in combination therapy, while the combination therapy of didox is yet to be evaluated. However, the agents which were more efficacious as monotherapy still

Table 9 Clofarabine clinical trials

Drug name	Trial design	Indication	Phase	Outcomes	Dose limiting toxicity (grade 3 or 4)	References
Clofarabine	Single agent	Acute leukemia	I	CR: 5/32 RR: 16%	Reversible hepatotoxicity	(Kantarjian et al. 2003)
	Single agent	Refractory non-Hodgkin lymphoma	I	CR: 8/30 PR: 6/30 RR: 47%	Neutropenia and thrombocytopenia	Abramson et al. (2013)
	Single agent	Relapsed acute lymphoblastic leukemia	II	CR: 12/61 PR: 6/61 PFS: 3 RR: 30%	Febrile neutropenia	Jeha et al. (2006)
	Single agent	Relapsed acute myeloid leukemia	II	CR: 1/42 PR: 10/42 RR: 26%	Febrile neutropenia	Jeha et al. (2009)
	Single agent	Myelodysplastic syndrome	II	CR: 1/9 PR: 1/9 HI: 2/9 SD: 3/9 RR: 44%	Severe pancytopenia	Lim et al. (2010)
	Combination with cyclophosphamide	Refractory acute leukemia	I	CR: 5/18 PR: 1/18 RR: 33%	Bone marrow aplasia	Karp et al. (2007)
	Combination with etoposide, cyclophosphamide	Refractory acute leukemia	I	CR: 16/25 RR: 64%	Hepatotoxicity	Hijiya et al. (2009)
	Combination with etoposide and mitoxantrone	Relapsed acute leukemia	1/II	CR: 5/22 CR with incomplete platelet recovery: 3/22 OS: 167 days RR: 36%	Myelosuppression and Neutropenia	Abbi et al. (2015)
	Combination with Busulfan and allogenic stem cell transplantation	Intermediate/high risk follicular lymphoma	II	CR: 12/14 RR: 86%	Mucositis, hand-foot syndrome	Farag et al. (2011)
	Combination with ara-C	Refractory acute lymphocytic leukemia	II	CR: 6/36 OS: 3 RR: 17%	Infection	Advani et al. (2010)
	Combination with ara-C	Refractory acute lymphoblastic leukemia	II	CR: 14/30 PR: 2/30 RR: 53%	Myelosuppression and neutropenia	Agura et al. (2011)
	Combination with ara-C (>55 years)	Refractory acute myelogenous leukemia	III	CR: 57/162 PR: 19/162 OS: 6.6 RR: 46.9%	Febrile neutropenia, hypokalemia, thrombocytopenia	Faderl et al. (2012)

CR complete response, *PR* partial response, *RR* response rate (CR + PR) in %, *SD* stable disease, *OR* objective response, *PFS* median progression-free survival (in months) unless otherwise indicated, *OS* median overall survival (in months), unless otherwise indicated, *TTP* median time to progression (in months), unless otherwise indicated

showed synergism in some drug combinations. For example, siRNA with temozolomide, triapine with fludarabine, didox with carmustine/temozolomide/melphalan, trimidox with tiazofurine/adriamycin/streptozotocin/*ara-C*/cisplatin/cyclophosphamide, or gallium maltolate with bortezomib exhibited synergism for a variety of cancers. Hydroxyurea is currently used more as combination therapy, even though

it was still efficacious as a monotherapy. The combination of hydroxy urea with *ara-C* was shown to exhibit synergistic anticancer activity.

Most of the RR1 inhibitors such as gemcitabine, cladribine, fludarabine, motexafin have been evaluated in phase III studies recently (Holowiecki et al. 2004; Mehta et al. 2009; O'Brien et al. 2009; Hallek et al. 2010; Robak

et al. 2010; Duenas-Gonzalez et al. 2011; Manegold et al. 2011) and shows promise for further development for variety of cancers. Clofarabine is currently in phase III studies (Foran 2014), while GTI-2501 has progressed up to phase II studies.

Currently RR1 inhibitors that have long been used in chemotherapy such as gemcitabine, cladribine, fludarabine and clofarabine are mostly used as a combination therapy, but is equally efficacious as a monotherapy also, except tezacitabine which did not progress beyond phase I trials. For example, the combination of fludarabine with *ara-C* or clofarabine with cyclophosphamide exhibited synergistic activity against a variety of cancers. Antisense therapy, such as GTI-2501 and redox mediator motexafin gadolinium are more efficacious as a monotherapy, while the combination therapy of motexafin gadolinium produced mixed results.

Based on the results of these clinical trials, we can conclude that RR1 and RR2 inhibitors still is a viable therapeutic option, either as a monotherapy or as a combination in cancer chemotherapy. With the recent advances made in cancer biology and molecular therapeutics, further development of several biological and small molecule chemical inhibitors of RR with improved efficacy and reduced toxicity is possible for the treatment of variety of cancers.

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