

Ranpirnase and its potential for the treatment of unresectable malignant mesothelioma

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Abstract: Ribonucleases are a superfamily of enzymes which operate at the crossroads of transcription and translation, catalyzing the degradation of RNA; they can be cytotoxic because the cleavage of RNA renders indecipherable its information. Ranpirnase is a novel ribonuclease which preferentially degrades tRNA, thus leading to inhibition of protein synthesis and, ultimately, to cytostasis and cytotoxicity. Ranpirnase has demonstrated antitumor activity both in vitro and in vivo in several tumor models. The maximum tolerated dose emerging from phase I studies was 960 g/m², with renal toxicity as the main dose-limiting toxicity. A large phase II trial showed that ranpirnase has disease-modifying activity against malignant mesothelioma. Ranpirnase proved to be superior to doxorubicin in a phase III trial, while preliminary results of another large, phase III trial, suggest that the combination of ranpirnase and doxorubicin could be more effective than doxorubicin alone. In all the above studies, ranpirnase seems to act mainly as a cytostatic rather than a cytotoxic drug, stabilizing progressive disease and potentially prolonging patients' survival. Ranpirnase may thus find its niche in combination with doxorubicin for mesothelioma as a second-line therapy, where no standard of care presently exists.

Keywords: ranpirnase, mesothelioma, ribonucleases, doxorubicin, antitumor activity

Malignant mesothelioma: still an orphan disease

The incidence of malignant mesothelioma (MMe), a relatively rare cancer linked to asbestos exposure, is expected to increase dramatically over the next couple of decades, both in Europe and in many developing countries (Peto et al 1999; Carbone et al 2007).

The vast majority of MMe patients present with stage III or IV, ie, mainly unresectable, disease; despite some recent advance in the medical treatment of MMe, presently the aim of the treatment for these patients is only palliation (Vogelzang et al 2005; Fennell et al 2008). A few randomized controlled trials have firmly established the use of antifolate-platinum doublets as the present treatment of choice for locally advanced unresectable or metastatic MMe patients, supporting the evidence from meta-analyses for the superior activity of platinum-based combinations (Fennell et al 2008).

Even though, theoretically, second-line therapy of MMe might have an important role in increasing survival rates, no standards have emerged so far in this setting.

Taken together, the unsatisfactory results obtained with first-line treatment options, and the lack of a standard of treatment for those patients who, still being in good condition, progress after a first-line treatment, emphasize the need for newer, active, agents for such a disease.

An historic introduction to ribonucleases

Ribonucleases, which were extensively studied in the 1960s and 1970s, are a family of enzymes well known for their physiological ability to cleave RNA; indeed, bovine

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pancreatic ribonuclease, or RNase A, has been used as a privileged model in protein folding studies. After this early enthusiasm, ribonucleases were almost dismissed as uninteresting digestive enzymes. Only recently have they attracted attention again, owing to their remarkable and complex biological activities (Leland and Raines 2001; Benito et al 2005; Arnold and Ulbrich-Hofmann 2006; Lee and Raines 2008).

As a whole, ribonucleases are a superfamily of secretory enzymes that operate at the crossroads of transcription and translation, catalyzing the degradation of RNA; however, several other intriguing activities have been described recently. For example, angiogenin is able to promote angiogenesis (Riordan 1997), and bovine seminal ribonuclease, a unique dimeric homolog of RNase A, has relevant immunosuppressive and antitumor activities, as well as being embryotoxic and aspermatogenic (D'Alessio et al 1997).

Ribonucleases: a novel class of anticancer targeted agents

Ribonucleases can be cytotoxic due to the fact that the cleavage of RNA renders indecipherable the information it encodes.

For years, replicative DNA was the main target of anticancer agents; more recently, specific proteins endowed

with receptor and/or signal transduction properties have become the main target of anticancer agents; RNA, which is in between DNA and proteins (Figure 1), only rarely has been the target of anticancer drugs (Bruserud 2007), and even then with only modest relevance, as in the case of 5-FU antitumor activity.

The cytotoxicity of pancreatic-type ribonucleases was first discovered and described in the early 1950s, when RNase A was shown to be toxic to tumor cells *in vitro* (Ledoux and Balthus 1954) as well as in *in vivo* models (Ledoux 1955).

Ranpirnase

Pharmacology and mechanism of action

Ranpirnase (P-30 protein [Onconase[®]], Alfacell Corp, Bloomfield, NJ, USA) is a novel ribonuclease which, as a homolog of RNase A, belongs to the family of pancreatic ribonucleases (Ardelt et al 1991); however, it is present in the oocytes and early embryos of *Rana pipiens*, the Northern Leopard frog (Irie et al 1998). It is a single-chain protein, 104 amino acid residues long, with a molecular weight of about 12,000 Da (Ardelt et al 1991), an amino acid sequence ~30% identical to that of RNase A (Ardelt et al 1991), and molecular structure similar to that of RNase A (Mosimann et al 1992). Owing to the presence of 4 disulfide bonds, 3 of which are conserved in RNase A, it is highly stable to heat,

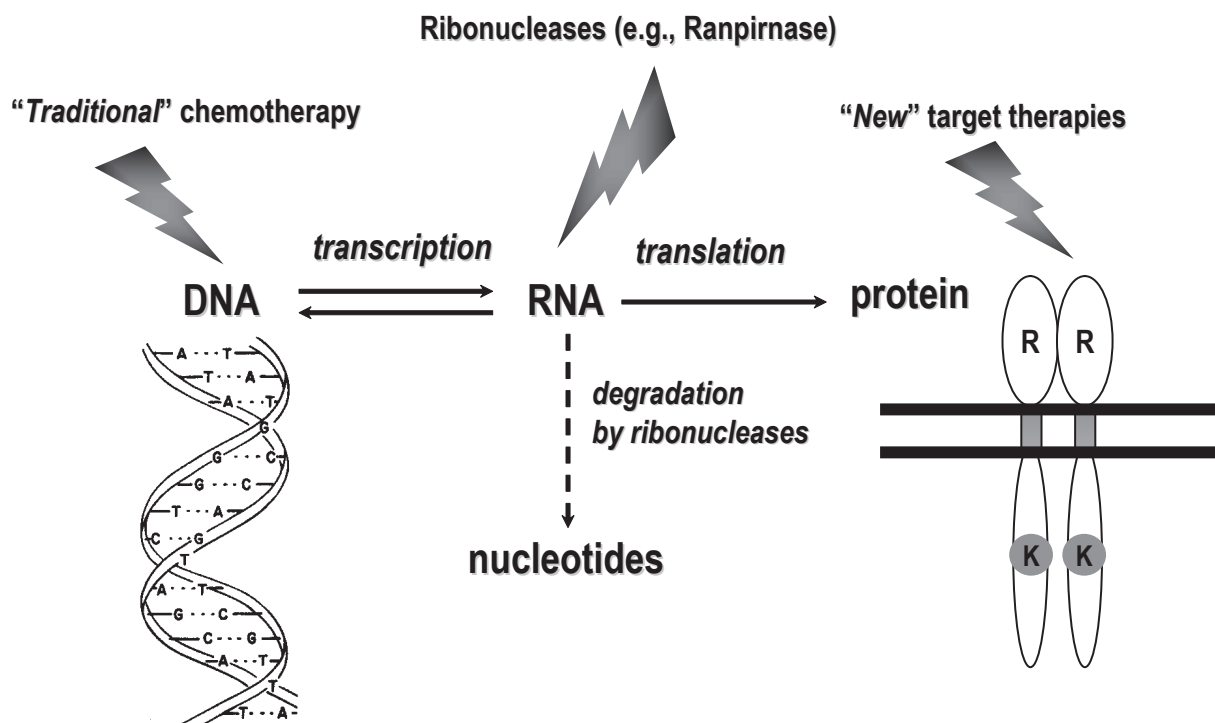


Figure 1 Anticancer agents usually target either DNA or proteins endowed with receptor and/or signal transduction properties. However, RNA, which is in between DNA and proteins, could also be targeted effectively by specific anticancer drugs such as ranpirnase.

with a midpoint temperature of thermal denaturation (T_m) of 90 °C, almost 30 °C higher than that of RNase A (Leland et al 1998).

Ranpirnase binds to the cell surface and uses the energy-dependent endocytic process to penetrate into the cell (Wu et al 1993), routed through the Golgi apparatus to the cytosol, where it preferentially degrades tRNA (but not ribosomal and mRNA) by catalyzing the cleavage of the P-O5' bond of RNA on the 3' side of pyrimidine nucleosides (Iordanov et al 2000a).

This RNA degradation leads to inhibition of protein synthesis and, ultimately, to the cytostatic and cytotoxic activity of ranpirnase. Indeed, ranpirnase plays a cytostatic role, arresting the cell cycle in G_1 (Darzynkiewicz et al 1988; Juan et al 1998), as well as a cytotoxic role, acting as a cytotoxin (Wu et al 1993). Evidence suggests that the irreparable tRNA damage induced by ranpirnase may constitute a pro-apoptotic signal (Iordanov et al 2000a); the apoptosis triggered by ranpirnase seems to be mainly caspase-dependent, even though a caspase-independent mechanism has been recently described (Michaelis et al 2007). Furthermore, p53 status does not affect ranpirnase-induced apoptosis (Costanzi et al 2005), a key feature of ranpirnase, since it is well known that many tumors carry an inactivated p53, which, in turn, can suppress or reduce the apoptotic process activated by several chemotherapeutic agents.

The superior activity of ranpirnase on tumor cells, compared with normal cells, has been explained molecularly by an elegant *in vitro* study by Iordanov et al (2000b), in which the authors investigated whether ranpirnase activates two signal-transduction pathways commonly stimulated by conventional chemo- and radio-therapy, ie, the stress-activated protein kinase (SAPK) and the nuclear factor- κ B (NF κ B) pathways. Ranpirnase proved to be a potent activator of SAPK1 (JNK-1 and -2) and SAPK2 (p38 MAP kinase), but not NF κ B; using explanted fibroblasts from mice containing targeted disruption of both *jnk-1* and -2 alleles, the authors found that JNKs are important mediators of ranpirnase-induced cytotoxicity. Surprisingly, after immortalization of these same cells with human papilloma virus 16 (HPV 16) gene products E6 and E7, additional proapoptotic pathways were activated, thus suggesting that, in cancer cells, ranpirnase is more proapoptotic, inducing several different pathways.

Notably, ranpirnase proved not to be a substrate for the MDR1 gene product p-glycoprotein (pGP), one of the major factors responsible for resistance to cytotoxic chemotherapy; indeed, at least one *in vitro* study demonstrated that the

cytotoxic effect of ranpirnase was unrelated to P-gp expression levels, with an IC_{50} of approximately 6×10^{-5} M in both wild-type as well as MDR1-transfected cancer cells (Rybak et al 1996).

Ribonuclease activity is regulated by the presence of cytosolic, class-specific, inhibitors of its enzymatic activity, globally known as ribonuclease inhibitor (RI). Even though the precise biological role of these inhibitors is still far from perfectly known, they act to protect cellular RNA if a ribonuclease inadvertently enters the cytosol (Hofsteenge 1997); remarkably, RI is not so powerful in inhibiting ranpirnase catalysis (Leland and Raines 2001). Indeed, the K_i value for the inhibition of ranpirnase by RI is estimated to be $\geq 10^{-6}$ M, which is more than 10^7 -fold greater than the K_d value for the RI-RNase A complex (Boix et al 1996).

Further insights into the antitumor activity of ranpirnase have been reported recently. Ardel et al (2007) suggested that ranpirnase is able to decrease the generation of reactive oxygen species, as well as the mitochondrial transmembrane potential *in vitro*, and that such a suppression of intracellular oxidative stress may contribute to the cytotoxic and pro-apoptotic activity of the drug, when combined with cytotoxic agents; indeed, even though oxidative stress is generally regarded as pro-apoptotic, it may also interfere with cancer chemotherapy, as demonstrated in a Burkitt's lymphoma model, where apoptosis induced by several chemotherapeutic agents, including doxorubicin, was inhibited by hydrogen peroxide (Shacter et al 2000). Therefore, the antioxidative function of ranpirnase has been regarded as an important element of its antiproliferative/cytotoxic activity towards cancer cells, and a possible mechanism of its well-documented synergism with other anticancer agents (Mikulski et al 1990, 1992; Rybak et al 1996; Deptala et al 1998).

Other studies suggest that ranpirnase could also act as a radiation sensitizer (Lee et al 2007a), and that such a novel activity is due, on the one hand, to the inhibition of oxygen consumption (QO_2) and, on the other, to the inhibition of sublethal damage repair, both *in vitro* and *in vivo* in a xenograft model of lung cancer (Lee et al 2000a; Kim et al 2007).

Finally, another recent study demonstrated that multiple, small doses of ranpirnase increased apoptosis and cytotoxicity of A549 non-small-cell lung cancer, both *in vitro* (Lee et al 2007b) and *in vivo* (Lee and Shogen 2008), thus suggesting the use of alternative schedules of the drug.

Preclinical activity

In vitro, ranpirnase has demonstrated both cytostatic and cytotoxic effects on several murine and human cell lines

(Costanzi et al 2005; Pavlakis and Vogelzang 2006), as a single-agent, as well as in combination with other agents. The prevalent type of response to ranpirnase observed in established human cancer cell lines is summarized in Table 1.

Against MME cell lines, ranpirnase has been shown to inhibit cell growth, both in vitro and in vivo (Costanzi et al 2005); indeed, it proved able to prolong survival of tumor-bearing mice, compared with controls, an activity that has been documented in many different xenograft models (Costanzi et al 2005). Table 2 summarizes ranpirnase activity in different animal models.

Enhanced cytotoxicity has been seen with co-administration of ranpirnase with several anticancer drugs, including tamoxifen (Mikulski et al 1990, 1992), cisplatin (Mikulski et al 1992; Lee et al 2007b), doxorubicin (Mikulski et al 1999), vincristine (Rybak et al 1996), and also with phosphatidyl inositol-3 kinase inhibitors (Ramos-Nino et al 2005).

Biodistribution and toxic effects in animals

Biodistribution studies in mice have shown that iv ranpirnase is taken up primarily by the kidneys (60%–70% of injected dose at 15 minutes), while liver uptake is minimal, although prolonged retention by the liver has been observed (Vasandani et al 1996). In the kidney, after 1 week of treatment, and more evidently after 3 weeks, there was evidence of acute moderate multifocal proximal renal tubular necrosis, a toxicity that was reversed 2 weeks after drug withdrawal; in the liver, toxic effects (once again reversible) were seen in the hepatocytes, with lipidosis, cellular swelling, vacuolar

degeneration and apoptosis in mice treated for 1 or 3 weeks (Vasandani et al 1999).

Phase I studies

Two phase I studies evaluating the optimum dose and schedule of ranpirnase have been performed. In the first of these studies, ranpirnase was studied using a daily schedule of iv administration beginning at 6 g/m²/day and closing at 105 g/m²/day, without determining a maximum tolerated dose (MTD). One patient developed renal failure requiring dialysis at the dose level of 80 g/m². Three (9.3%) of the 32 patients enrolled showed disease stabilization as their best response to treatment (Costanzi et al 2005).

In the second phase I study, ranpirnase was administered iv as a single agent on a weekly schedule at 5 dose levels, in the range of 60–1200 g/m². A total of 71 patients were thus treated, and the MTD was established as 960 g/m². In this study, some objective responses were observed in lung cancer (1 partial response), esophageal carcinoma (1 partial response), and colorectal carcinoma (1 minor response) patients, while stable diseases were observed in other patients with different tumors. Thus, the recommended phase II dose using this weekly schedule was 480 g/m²/week (Mikulski et al 1993).

In the phase I study of the weekly schedule, the dose-limiting toxicity was renal, manifested by proteinuria with or without azotemia, peripheral edema, and fatigue. Other toxicities included flushing, myalgias, transient dizziness, and decreased appetite. Transient hypotensive reactions preceded by flushing that responded quickly to volume expansion were also observed. Notably, no significant myelosuppression, mucositis, alopecia, cardiotoxicity, coagulopathy, or hepatotoxicity was observed.

Table 1 Prevalent type of response to ranpirnase observed in established human cancer cell lines in vitro

Human cell line	Author	Prevalent type of response to ranpirnase observed
A549 (NSCLC)	Lee et al 2000	cytotoxic
ASPC-1 (pancreas)		
HepG2 (hepatoma)		
LS174T (colon)	Halicka et al 1996	pro-apoptotic
U937 (lymphoma)		
HL 60 (leukemia)		
Colo 320 CM (colon)	Darzynkiewicz et al 1988	cell cycle delay (all phases) or arrest
A-253 (submaxillary carcinoma)		
HL 60 (leukemia)		
U937 (histocytic lymphoma)	Juan et al 1998	cell cycle arrest in G ₁

Table 2 In vivo activity of ranpirnase in animal models

Model	Author	Prevalent activity
HT29 ^{MDR1} colon cancer xenograft	Rybak et al 1996	In association with vincristine, ranpirnase overcame MDR1-mediated resistance
M109 Madison mouse carcinoma in mice	Mikulski et al 1990	Ranpirnase slowed tumor growth, increasing survival (in the Madison mouse model)
MDA-MB-231 human breast cancer in nude mice	Mikulski et al 1999	Ranpirnase synergized with doxorubicin, increasing survival
Daudi cells given intraperitoneally in SCID mice	Newton et al 2001	Ranpirnase synergized with the anti-CD22 monoclonal antibody epratuzumab, increasing survival
H4IIE rat hepatoma MCalV murine adenocarcinoma FSall murine fibrosarcoma DU145 human prostate cancer in nude mice	Lee et al 2000b	Ranpirnase inhibited tumor growth
AsPC-1 human pancreatic carcinoma in nude mice	Lee et al 2003	

Phase II studies in tumors other than mesothelioma

Ranpirnase has been studied in phase II trials as a single agent in patients with non-small-cell lung cancer (Costanzi et al 1995; Mikulski et al 1995), breast cancer (Puccio et al 1996), and renal cell cancer (Vogelzang et al 1999), and in combination with tamoxifen in pancreatic (Chun et al 1995) and prostate cancer (Costanzi et al 2005).

In the preliminary report of the phase II study in non-small-cell lung cancer, ranpirnase (given at 240 g/m²) as a single agent induced no objective responses in the 30 patients evaluated; however, 5 patients (17%) achieved disease stabilization, with a resulting median survival time of 7.7 months (Costanzi et al 1995; Mikulski et al 1995).

A small study, reported in abstract form (Puccio et al 1996), demonstrated a limited clinical benefit in breast cancer (1 minor response and 2 disease stabilizations out of 17 patients).

In 14 patients with refractory advanced renal cell cancer, ranpirnase, given at a dose of 480 g/m²/week, proved to be inactive in terms of antitumor activity, but yielded encouraging results in terms of median survival time (Vogelzang et al 1999).

In a phase I/II pancreatic cancer study, ranpirnase recommended dose was 480 mg/m², while tamoxifen was started 7 days prior the first ranpirnase dose to allow for the accumulation of the drug within the tumor, as suggested by a pre-clinical model; such a combination yielded 1 complete, 2 minor responses, and 7 disease stabilizations out of 32 evaluable patients, suggesting a potential activity of the combination in pancreatic cancer (Chun et al 1995; Costanzi et al 2005).

Another study addressed the antitumor activity of ranpirnase when given in combination with tamoxifen in patients with early prostate cancer recurrence, as evidenced by rising prostate specific antigen (PSA) test after prostatectomy or radiation therapy. The study has not been reported in extenso so far, having been addressed only within the review by Costanzi et al (2005). Among the 13 patients enrolled in this small study, 6 discontinued treatment owing to toxicity before completing 3 cycles of treatment, and only 1 patient showed stable PSA levels, suggesting an extremely low activity of the of the ranpirnase/tamoxifen combination in this setting.

Phase II study in malignant mesothelioma

A single-arm, open-label, multicenter phase II trial of ranpirnase as a single agent has been performed in MME patients, the largest phase II study of this drug undertaken (Mikulski et al 2002).

The aim was to evaluate the drug's clinical efficacy and safety in this orphan disease; survival was the primary end point, while secondary end points were tumor response and time to progression. All patients received weekly iv infusions of ranpirnase at an initial dose of 480 g/m².

Patients (n = 105) with an ECOG performance status score of 0–2, were enrolled; the Cancer and Leukemia Group B (CALGB) prognostic group criteria (Herndon et al 1998) were used to define treatment target groups (TTGs). This study prospectively used an intent-to-treat (ITT) analysis that included all patients enrolled, and retrospectively used the TTG analysis that included only those patients who met the predefined criteria for the CALGB prognostic groups

1–4 combined ($n = 81$). Using the Kaplan-Meier method, the overall median survival time was 6 months (95% confidence interval [CI]: 4.7–10.0 months) and 8.3 months for the ITT populations; the 1- and 2-year survival rates were 34.3% and 21.6%, respectively, for the ITT population, and 42% and 26.8% for TTG, respectively. The median survival times for the CALGB groups 1–6 were 29.9, 6.6, 5.8, 10.7, 4.5, and 1.8 months, respectively. As expected, survival was longest for the best prognostic group and shortest for the worst group. Survival analysis of patients who had prior chemotherapy vs those who had not was not significantly different (median survival time: 7.3 vs 5.7 months; 1-year survival rate: 33.3 versus 34.9%; 2-year survival rate: 19.7 vs 22.7%; log-rank $p = 0.971$). Patients with better performance status and epithelioid histology had, as expected, more favorable survival. Among the 81 patients assessable for investigator-assessed tumor response, 4 had partial responses (PR), 2 had minor responses (MR), and 35 experienced disease stabilization (SD) (Mikulski et al 2002).

Twenty-two patients developed grade 3 ($n = 18$) or 4 ($n = 4$) adverse events that were considered related to treatment. As expected on the basis of the phase I experience, treatment was associated with asthenia, flu-like symptoms, arthralgia, fever, vasodilation (manifesting as flushing with occasional hypotension and/or vasovagal reaction), paraesthesias, peripheral edema, renal insufficiency, and allergic reactions.

This study clearly suggested that ranpirnase mainly acts as a cytostatic agent, as do many other molecularly targeted drugs. Indeed, conventional radiological measurements and commonly used response criteria (eg, the RECIST ones) are not the best way to evaluate the antitumor activity of drugs such as ranpirnase, time-dependent end points being more useful (Korn et al 2001; Pavlakis and Vogelzang 2006).

As a whole, this phase II trial in MMe clearly suggested that ranpirnase may have disease-modifying activity in MMe, justifying the subsequent move to phase III.

Phase III studies in malignant mesothelioma

Based on positive combination preclinical studies, ranpirnase could be combined with either cisplatin or doxorubicin, both established active agents for MMe (Vogelzang et al 2005; Fennel et al 2008). However, in view of its potential for renal toxicity, doxorubicin seemed the obvious choice for combination in order to avoid potential overlapping renal toxicity with cisplatin.

Thus, in an initial phase III study in MMe, patients were randomized to receive ranpirnase (480 g/m² iv weekly)

or doxorubicin (60 mg/m² iv q21 days) using a 3:2 randomization ratio (Vogelzang et al 2000). This was an open-label, multi-center, randomized controlled trial which enrolled 154 patients with MMe who were either chemotherapy-naïve or had failed one prior chemotherapy regimen; patients were stratified by performance status (0 vs 1) and histology (epithelioid vs non-epithelioid). The primary end point of the study was overall survival by ITT.

Final results (available on 144 patients, 75 treated with ranpirnase and 69 with doxorubicin), showed no significant differences between the two arms (Table 3a).

Analysis by CALGB prognostic groups, however, revealed an excess of poor prognosis patients (groups 5 and 6) in the ranpirnase arm (37%) compared with the doxorubicin arm (17%).

A post-hoc analysis was thus performed excluding these patients and those with unconfirmed MMe by centralized pathological review (additional $n = 5$). TTGs were defined based on the CALGB prognostic groups, as evaluated in the above-mentioned phase II study. The results of this analysis clearly favored ranpirnase, as shown in Table 3b; indeed, a Cox proportional hazards regression analysis revealed a survival risk ratio of 1.34 in favor of ranpirnase treatment in the ITT population, allowing for histology, age, sex, CALGB prognostic groups and abdominal involvement (95% CI: 0.93–1.94; $p = 0.12$). In the post-hoc TTG analysis, the same Cox proportional hazards regression analysis revealed a survival risk ratio of 1.60 in favor of ranpirnase treatment (95% CI: 1.03–2.50; $p = 0.04$).

Few grade 3/4 toxicities were observed (Table 4), the most commonly reported being asthenia (10.8%), and ranpirnase toxicities were mainly reversible on drug discontinuation (Vogelzang 2000). Furthermore, owing to protocol-mandated dose reduction for renal toxicity, no serious renal toxicity

Table 3 Results of the first phase III trial of ranpirnase vs doxorubicin in MMe patients according to the patient population considered: ITT (a) or TTG (b) (Vogelzang 2000)

a	Ranpirnase-treated patients	Doxorubicin-treated patients
Median survival	8.4 months	8.2 months
1-year survival rate	33.3%	34.8%
2-year survival rate	13.7%	10.9%
b	Ranpirnase-treated patients	Doxorubicin-treated patients
Median survival	11.6 months	9.6 months
1-year survival rate	46.8%	38.6%
2-year survival rate	20.9%	13.2%

Table 4 Grade III and IV toxicities observed in the phase III study of ranpirnase vs doxorubicin in MMe (according to the National Cancer Institute of Canada [NCIC] classification) (Vogelzang 2000)

Toxicity	Ranpirnase			
	G3		G4	
	no.	%	no.	%
Asthenia	9	10.8	1	1.2
Arthralgia/myalgia	4	4.8	0	0
Paresthesias	4	4.8	0	0
Dyspnea	4	4.8	0	0
Edema	2	2.4	0	0
Anaphylactoid reaction	0	0	1	1.2
Nausea and vomiting	0	0	1	1.2
Toxicity	Doxorubicin			
	G3		G4	
	no.	%	no.	%
Asthenia	2	4.5	0	0
Fever	2	4.5	1	2.3
Anorexia	1	2.3	0	0
Mucositis	1	2.3	0	0
Nausea and vomiting	1	2.3	1	2.3

was observed, thus supporting the view that ranpirnase, when administered with appropriate attention for hypersensitivity and with monitoring and dose adjustment for renal impairment, is a relatively safe and well-tolerated treatment (Pavlakis and Vogelzang 2006).

After the aforementioned phase III trial, another multicenter, randomized, controlled, phase III study, to be performed on a global scale, was designed: the P30–302 protocol, entitled “Onconase® plus Doxorubicin versus Doxorubicin alone for patients with malignant pleural or peritoneal mesothelioma who have had no more than one prior chemotherapy regimen”.

In this study, patients with proven mesothelioma were randomized to receive either doxorubicin 60 mg/m² iv every 3 weeks or iv ranpirnase weekly (given at 240 g/m² in cycle 1, to be escalated to 480 g/m² from cycle 2 in the absence of serious toxicity), followed by doxorubicin 60 mg/m² iv every 3 weeks. Patients were stratified according to the CALGB prognostic groups (1–4) and histology, and were randomized in a 1:1 fashion. The primary end point of the study was overall survival. This study has been recently closed to enrollment, but its final results are not yet available.

An interim analysis was performed per protocol at the occurrence of 105 deaths. The key findings were as follows (pers comm., Shogen K).

Overall median survival time (MST), the primary endpoint of the study, favored the ranpirnase plus doxorubicin treatment group (12 months) over the doxorubicin group (10 months). A 2-month improvement in median survival has also been observed previously in the TTG analysis (N = 104) from the completed phase III single agent study that favored the ranpirnase group over the doxorubicin group (11.6 months vs 9.6 months).

Other results of this interim analysis included: at 1 year, 47% of the ranpirnase plus doxorubicin-treated subjects were alive compared with 36% of patients treated with doxorubicin only. Subjects evaluable for clinical response (those with evidence of tumor regression or stabilization of disease for a minimum of 3 months) showed a 7-month difference in MST (17 vs 10 months) favoring the ranpirnase plus doxorubicin group vs the doxorubicin group.

The analysis of safety data revealed that ranpirnase, when given with doxorubicin, did not increase the number or severity of known doxorubicin-associated side effects. The most frequent side effects reported for both treatment groups included nausea, fatigue, and alopecia. The incidence of these events was comparable for both treatment groups.

Conclusions

Ranpirnase is a ribonuclease endowed with potent antitumor properties; its mechanism of action is completely novel since, by degrading tRNA, it acts both as a cytotoxic and a cytostatic drug; furthermore, owing to both its in vitro synergy with other cytotoxic agents, and its tolerability as a single agent, it is amenable to combination with traditional chemotherapeutic drugs, eg, doxorubicin and cisplatin.

Since its early clinical development, it has held great promise for the treatment of MMe, where it seems to act mainly as a cytostatic agent, thus stabilizing the disease. Indeed, ranpirnase proved to be superior to doxorubicin within a phase III trial, while preliminary results of another large, phase III trial suggest that the combination of ranpirnase and doxorubicin could be more effective than doxorubicin alone.

Ranpirnase appears to be generally well tolerated with predictable and reversible toxicity, and with very few serious adverse events; furthermore, dose modifications are usually required only for changes in renal function.

Unfortunately for the development of the drug, during the course of its phase III development, the combination of pemetrexed and a platinum derivative emerged as the standard first-line treatment for MMe patients in. This led to a slowing of the recruitment into the P30–302 protocol

and clearly reduced the interest for its use as a first-line treatment.

Thus, while waiting the final results of the above study, it appears clear that ranpirnase may find its niche (in combination with doxorubicin) for second-line therapy of MMe (Pavlakakis and Vogelzang 2006) where, at present, no standard of care exists.

However, the current understanding of its mechanism of action, coupled with its favorable toxicity profile, characterized by a lack of major toxicities, especially in terms of hematology, make ranpirnase an appealing drug to use in combination with other anticancer agents, as well as with radiotherapy. This could clearly open a new frontier for the use of this novel drug in tumor types other than MMe.

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Disclosures

None of the authors has any conflicts of interest to disclose.

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