Decitabine in myelodysplastic syndromes

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Decitabine (5-aza-2’-deoxycytidine), a cytosine analog, inhibits DNA methylation and has dual effects on neoplastic cells, including the reactivation of silenced genes and differentiation at low doses, and cytotoxicity at high doses. Decitabine has promising clinical efficacy in the treatment of myelodysplastic syndromes (a heterogeneous group of bone marrow malignancies), with evidence of target modulation (hypomethylation) and a favorable toxicity profile. Optimal dosing schedules of decitabine in myelodysplastic syndrome are those that maximize hypomethylation (low dose, high dose intensity, multiple cycles). However, the molecular mechanisms of in vivo response to decitabine are still unclear. Combination therapies that augment decitabine’s epigenetic effect, or take advantage of gene activation, will likely improve clinical responses and may extend its use to the treatment of other malignancies.

The development of new therapeutic strategies for the myelodysplastic syndrome (MDS) has been the result of extensive understanding of the pathobiology of the disease. Therapeutics targeting chromatin structure, angiogenesis and the microenvironment that nurtures the MDS phenotype have demonstrated significant activity and offer an opportunity to alter the natural history of the disease [1]. Chromatin remodeling is a powerful mechanism of regulating gene expression and protein function [2]. In extreme states, chromatin remodeling can permanently repress the expression of a gene – a situation termed epigenetic silencing. Such silencing is exploited by cancers to fully express the malignant phenotype [3]. Evidence supporting a role of epigenetic gene silencing in tumorigenesis stems from studies revealing a large number of genes that are silenced by aberrant DNA methylation in different types of cancers – many of which are involved in the control of cell-cycle progression, apoptosis, tissue invasion and genomic stability. DNA methylation is remarkably altered in most malignancies, with concomitant global and localized hypermethylation [4]. This increased methylation affects mainly CpG islands located in regulatory regions such as gene promoters, and often suppresses gene expression permanently, providing cancers with an alternative to mutations or deletions for the inactivation of tumor-suppressor and other critical genes. Indeed, leukemias and MDS are characterized by the hypermethylation and silencing of multiple genes [5,6]. This process can occur early in the disease course and is also associated with disease progression. The cyclin-dependent kinase inhibitor p15 was described as a frequent target of aberrant methylation in MDS and its inactivation is associated with an increased risk of progression to acute myeloid leukemia (AML) [7]. Other similar genes were also described and their aberrant methylation was associated with resistance to chemotherapy [8,9].

Azacitidine (5-azacitidine) and decitabine (5-aza-2’-deoxycytidine) are cytosine analogs synthesized in the 1960s with demonstrated in vitro anti-leukemic activity [5]. Azacitidine was recently approved by the US Food and Drug Administration (FDA) for the treatment of MDS and has been extensively reviewed [14–16]. This article focuses on the role of decitabine in the treatment of MDS.

Mechanism of action
Decitabine is a deoxycytidine analog which is phosphorylated and incorporated into DNA. Once incorporated, it covalently binds to DNA
methytransferases and traps the enzymes to DNA, acting as an irreversible inhibitor of their enzymatic activity. As a result, decitabine produces marked DNA hypomethylation in vitro and in vivo [17]. Through hypomethylation induction, decitabine restores silenced gene expression. The precise molecular mechanism of this phenomenon is increasingly being deciphered. A number of studies have illustrated a cascade of biochemical events triggered by promoter DNA methylation that involves initial DNA binding proteins, which attract histone deacetylases and histone methylases that eventually modify histones into a silenced chromatin state [18,19]. Moreover, a feedback loop appears to be evident between DNA methylation and histone methylation whereby each of these biochemical modifications at a given gene triggers the other, thus creating a self-reinforcing silencing loop [19]. This silencing loop is interrupted by decitabine. Thus, treatment of neoplastic cell lines with decitabine has been shown to induce hypomethylation and reverse the silenced histone code rapidly at tumor-suppressor gene loci [20–22]. This dual effect (hypomethylation–histone changes) explains the superiority of decitabine on gene expression activation, compared with the histone-deacetylase inhibitors [23]. Decitabine also has significant effects on the expression of genes that are not silenced by CpG island methylation. Decitabine induces the expression of p21, a gene that shows no DNA hypermethylation in cancer [24]. At a molecular level, the effects of decitabine on the histone code are not limited to genes showing silencing by promoter-associated methylation [22], for example the histone H3-lysine 9 acetylation:methylation ratio was significantly increased by decitabine treatment of neoplastic cells at genes showing no DNA hypermethylation. This silencing-independent activity of decitabine remains incompletely understood. Some of the changes could be reactive, related to the stresses of exposing cells to a potentially cytotoxic agent. Nevertheless, the ultimate antineoplastic mechanism of action for decitabine could be very pleiotropic and deserves further investigation.

**Pharmacology & pharmacokinetics**

Given that the antineoplastic action of decitabine is a result of its incorporation into newly synthesized DNA, it is an S phase-specific agent [11]. At low doses, it does not block cell cycle progression of G1-phase cells into the S phase. In clonogenic assays, a 1 h exposure at a concentration of 10 µm of decitabine produces a loss of clonogenicity in the same range of cells in the S phase (30–50%). A longer exposure time of 24 h showed a markedly higher antineoplastic activity, with greater than 95% loss of clonogenicity, using a dose of 1 µm [25]. In plasma and cerebrospinal fluid (CSF) pharmacokinetic assays, the half-life of decitabine was between 39 and 144 min depending on the animal model, and decitabine concentrations in the CSF were 27 to 58% of the plateau plasma concentration [11]. However, the intracellular half-life of decitabine, particularly after DNA incorporation, is not known and maybe considerably higher. Oral administration of decitabine is not optimal due to rapid decomposition of this analog in acid [11].

**Clinical trials**

**Phase I studies**

Decitabine has been in clinical trials for over two decades [5]. The original studies were classical Phase I trials which identified the maximally tolerated dose (MTD) as 1500 to 2250 mg/m² [26,27]. The dose-limiting toxicity was primarily hematologic. Phase II studies were disappointing in solid tumors [28], but more promising in AML, MDS and CML.

The first clinical studies of decitabine in hematologic malignancies used 1500 to 2500 mg/m²/course. Response rates with decitabine as a single agent or in combination with other therapies were 30 to 60% [13,26,27,29–31] (Table 1). Despite promising activity, high-dose decitabine regimens were not pursued because of delayed and prolonged myelosuppression. At these doses, the drug is likely to be working as a cytotoxic cytosine nucleoside analog, and its superiority in that regard to cytarabine was not clear. Decitabine at a lower dose schedule (15 mg/m² three times a day for 3 days) was reported to have encouraging activity in MDS [32]. An even lower dose (0.15 mg/kg/day over 1 h for 10 days) was reported to have biological efficacy in reactivating hemoglobin F in patients with sickle cell disease, with relatively little toxicity [33]. These observations, combined with the short half-life of the drug and its absolute requirement for DNA synthesis for activity, led to a novel Phase I trial of decitabine in patients with relapsed or refractory leukemia, testing low-dose longer exposure schedules with the intent of finding an ‘optimal dose’ for responses other than the MTD [34]. A total of 50 patients (44 with AML/MDS, five with CML and one with acute lymphoblastic leukemia
Decitabine – DRUG PROFILE

[ALL]) were treated with increasing doses of decitabine (5, 10, 15 and 20 mg/m²) intravenously over 1 hr daily, 5 days a week for 2 consecutive weeks. The starting dose per course in this study was thus 30 times less than the MTD. The duration was then increased to 15 and 20 days. The treatment was well tolerated, with myelosuppression being the major side effect. Responses were seen at all dose levels evaluated. Overall, there were nine complete responses (CR), one partial response (PR) and three hematologic improvements (HI). In that study, the most striking finding was that patients treated at higher cumulative doses had a lower response rate. This low response rate at high doses was consistent with earlier studies. Recent studies have also evaluated decitabine as a continuous infusion in MDS [35] as well as in solid tumors [36]. These dose schedules were generally found to be less effective and/or more toxic (myelosuppression) than bolus intravenous schedules.

Phase II studies

Two relatively large Phase II studies of decitabine in MDS were recently reported (Table 2). Wijermans and colleagues reported on several studies conducted in Europe of decitabine in MDS [32,35,37]. In these studies, 169 older patients (median 70 years) with intermediate or high-risk MDS were treated with a relatively low dose of decitabine (135 mg/m² total dose/course). The overall response rate was 49% and the induction death rate was 7%. A remarkable response in the platelet count was seen, with 63% of the patients showing a significant platelet increment after at least two cycles [38]. The median duration of response was 9 months and the median survival 15 months, with a 2-year survival rate of 34%. Clinical complete remissions were also associated with cytogenetic remissions [39]. Survival was better for patients achieving a cytogenetic response compared with those who did not. Preliminary results of another Phase II trial of decitabine in MDS were recently reported in abstract form [40]. The study was a randomized Phase II trial of decitabine, testing both the dose intensity and subcutaneous route of administration. Patients received a total dose of 100 mg/m²/course, and were randomized in a Bayesian design to three groups consisting of:

- 10 mg/m²/day intravenously over 1 h for 10 days
- 20 mg/m²/day intravenously over 1 h for 5 days
- 20 mg/m³/day subcutaneously for 5 days (two doses)

Cycles were administered every 4 weeks and responses evaluated after 3 cycles. A total of 63 evaluable patients were reported on, with a median age of 66 years (range 39–90 years), 21% had secondary MDS and 57% had unfavorable cytogenetics. The overall response rate was reported to be 82% (CR: 37%; PR: 8%; marrow CR: 20%; clinical benefit: 16%). Based upon the treatment schedule, 47% of patients in the intravenous (5-day treatment group) achieved a CR compared with 29%, and 24% of patients randomized to the subcutaneous group and intravenous (10-day treatment) groups, respectively.

Table 1. Selected decitabine Phase I and II clinical trials in myeloid malignancies.

<table>
<thead>
<tr>
<th>Decitabine therapy</th>
<th>n</th>
<th>Response</th>
<th>Nonhematologic toxicity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75–80 mg/kg i.v. for 8–44 h</td>
<td>30</td>
<td>10% marrow response</td>
<td>Mild diarrhea, alopecia</td>
<td>[27]</td>
</tr>
<tr>
<td>45–100 mg/kg i.v. for 40–90 h</td>
<td>27</td>
<td>22% CR</td>
<td>Mild nausea, vomiting, mucositis</td>
<td>[26]</td>
</tr>
<tr>
<td>45–270 mg/m² i.v. over 9–12 h x 3 days</td>
<td>27</td>
<td>15% CR</td>
<td>Grade III hepatic, GI, renal, pulmonary</td>
<td>[50]</td>
</tr>
<tr>
<td>270–360 mg/m² i.v. over 3–4 h x 3 days</td>
<td>12</td>
<td>25% CR</td>
<td>No grade III-IV</td>
<td>[29]</td>
</tr>
<tr>
<td>45–50 mg/m² i.v. x 3 days</td>
<td>10</td>
<td>50% HI</td>
<td>Nausea/vomiting, peritonitis</td>
<td>[30]</td>
</tr>
<tr>
<td>250 mg/m² x 6 days with amsacrine 120 mg/m² on days 6–7, or idarubicin 12 mg/m² on days 5–7</td>
<td>22</td>
<td>59% CR</td>
<td>Nausea/vomiting, diarrhea, peritonitis, CNS toxicity, weight loss, GI bleed</td>
<td>[31]</td>
</tr>
<tr>
<td>5–20 mg/m² i.v. over 1 h x 10–20 days</td>
<td>50</td>
<td>18% CR, 14% PR</td>
<td>Hepatotoxicity</td>
<td>[34]</td>
</tr>
</tbody>
</table>

CR: Complete response; GI: Gastrointestinal; HI: Hematologic improvement; i.v.: Intravenous; PR: Partial response.
demonstrating that, within low-dose schedules, the most dose-intensive regimens were clinically superior. The side-effect profile was favorable and included primarily myelosuppression.

**Phase III studies**

A Phase III study of decitabine versus supportive care in patients with advanced MDS was recently reported in abstract form (Table 2) [41]. A total of 170 patients were randomized to decitabine versus supportive care. Decitabine was administered as a 3-h infusion of 15 mg/m² every 8 h for 3 days, with cycles repeated every 6 weeks for up to ten cycles (135 mg/m²/cycle). The groups were comparable for several risk factors, including:

- Age
- Cytogenetics
- Time from diagnosis
- International prognostic scoring system (IPSS) score
- Secondary MDS (14%)

Decitabine resulted in a higher OR rate (17%; CR: 9%; PR: 8 vs. 0%; p < 0.001), with median response duration of 9 months. Responses were obtained after a median of 3 months of therapy. The median survival of responders (CR and PR) was 678 days compared with 406 days in nonresponders (p = 0.038). Overall, as an intent-to-treat analysis, there was a nonsignificant trend for longer time-to-AML transformation or death (338 days in the decitabine group vs. 263 days in the supportive care group, p = 0.2). Subgroup analysis indicated a greater benefit in IPSS INT-2/high risk patients. All patients who responded to decitabine had higher quality of life scores, and myelosuppression was the primary toxicity reported. A Phase III multicenter trial comparing the same dose/schedule of decitabine with supportive care in elderly patients (age > 60 years) with MDS is currently being performed by the European Organization for Research and Treatment of Cancer (EORTC).

**In vivo molecular effects of decitabine**

Global hypomethylation after decitabine therapy in vivo was observed in early trials, thus confirming target modulation [42]. This has been studied in more detail in recent studies in AML and CML [17,34]. Hypomethylation after decitabine was dose dependent, peaked 10 to 15 days after a

<table>
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<tr>
<th>Dose</th>
<th>Patient characteristics</th>
<th>Response</th>
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<tbody>
<tr>
<td>50–75 mg/m²/day CI x 3 days every 6 weeks</td>
<td>Median age (range) (years): 72 (58–82)</td>
<td>n: 29</td>
</tr>
<tr>
<td>40 mg/m²/day CI x 3 days every 6 weeks</td>
<td>Median duration: ≥31 weeks</td>
<td>Median survival: 46 weeks</td>
</tr>
<tr>
<td>15 mg/m² t.i.d. i.v. over 4 h x 3 days every 6 weeks</td>
<td>Median age (range) (years): 68 (38–84)</td>
<td>n: 66</td>
</tr>
<tr>
<td>45–50 mg/m²/day i.v. over 4 h x 3 days every 6 weeks</td>
<td>Median duration: 31 weeks</td>
<td>Median survival: 15 months</td>
</tr>
<tr>
<td>20 mg/m²/day i.v. over 1 h x 5 days every 4 weeks</td>
<td>Median age (range) (years): 66 (39–90)</td>
<td>n: 63</td>
</tr>
<tr>
<td>vs. 10 mg/m²/day i.v. over 1 h x 10 days every 4 weeks</td>
<td>Median duration: NR</td>
<td>Median survival: NR</td>
</tr>
<tr>
<td>vs. 10 mg/m² b.i.d. sc. x 5 days every 4 weeks</td>
<td>Median age (range) (years): 70 (38–89)</td>
<td>n: 169</td>
</tr>
<tr>
<td>(n = 17)</td>
<td>Median duration: 40 weeks</td>
<td>Median survival: 15 months</td>
</tr>
<tr>
<td>15 mg/m² i.v. over 3 h t.i.d. x 3 days every 6 weeks</td>
<td>Median age (range) (years): NR</td>
<td>n: 89</td>
</tr>
<tr>
<td></td>
<td>Median duration: ≥9 months</td>
<td>Median survival: NR</td>
</tr>
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* Includes updated results of patients enrolled in the two previously reported trials.

b.i.d.: Twice daily; CI: Confidence interval; CR: Complete response; HI: Hematologic improvement; IPSS: International prognostic scoring system; i.v.: Intravenous; MDS: Myelodysplastic syndrome; NR: Not reported; OR: Overall response; PR: Partial response; sc.: Subcutaneous t.i.d.: Three-times daily.
10-day course and recovers to baseline at 4 to 6 weeks. Hypomethylation after cycle 1 showed an inconsistent association with response, with a positive correlation in AML, but an inverse correlation in CML. It was hypothesized that the inverse correlation between hypomethylation and response could be due to a cell death mechanism of response and resistance, whereby resistant cells can withstand more hypomethylation.

Daskalakis and colleagues studied p15 methylation in DNA extracted from bone marrow mononuclear cells from patients with MDS treated with decitabine [43]. They found demethylation in serial samples in nine out of 12 patients treated, and evidence of p15 gene reactivation by immunohistochemistry in four patients with low baseline expression. This reactivation was observed in responding patients, and indeed, the authors show evidence of gene reactivation in morphologically dysplastic cells in patients who were not in complete remission at the time of examination, demonstrating in vivo the potential of this drug. However, this effect may require multiple cycles of the drug. In a recent study, p15 hypomethylation after one cycle of decitabine was observed, however there was no correlation between p15 methylation at baseline or after therapy, and response [34].

The effects of decitabine on gene expression in vivo remain to be well characterized. In addition to effects on silenced tumor-suppressor genes, it will be important to also look at a broad variety of potential targets. In vitro, decitabine has been shown to activate genes that do not show promoter CpG island methylation (e.g., p21) [24], and gene expression microarrays have also revealed activation of a number of genes that do not have promoter-associated CpG islands [44]. It is distinctly possible that the therapeutic effects of this drug involve more than simple induction of tumor-suppressor gene hypomethylation and such studies will help elucidate these issues.

Expert commentary & outlook
Given that MDS is primarily a disease of older individuals, aggressive therapies such as combination chemotherapy and stem cell transplantation are simply not realistic for most patients. There is much interest therefore in exploring less toxic agents in this disease, and learning how to integrate them in a multigent therapeutic approach. It is obvious from the above data that decitabine, especially at lower doses, has significant effects in MDS. However its potential as an epigenetic drug has just begun to be investigated and several questions remain unanswered.

The issue of optimal dosing of this agent is under evaluation and still unclear, given that decitabine has dual activity (hypomethylating at low doses, cytotoxic at high doses). Here, the classical MTD route to drug development is not appropriate, and may have hindered the full evaluation of the drug. Indeed favorable responses were reported at doses ten to 30-times lower than the MTD in patients with MDS, and it is not clear that higher doses are beneficial clinically. Correlative studies suggest that the in vitro observation of rapid saturation of the hypomethylation effect (and loss of the differentiation effect) with increasing doses is also true in vivo [10]. Moreover, it was recently reported that greater hypomethylation and greater clinical efficacy were the result of a better dose intensity of decitabine. The sum total of dose-finding studies suggest that:

- Short bolus infusions are better than continuous infusion schedules
- Lower doses are better than high doses
- Dose intensity results in higher responses

Pharmacologically, these data could be explained by a correlation between peak levels of the drug and responses – an issue that deserves investigation. Simply put, a high dose of the drug is required for intracellular incorporation, after which the intracellular half-life of the drug may be long enough to achieve a therapeutic effect. It remains to be seen whether 20 mg/m² over 1 h is optimal to achieve hypomethylation, and how many days are required. The issue of optimal treatment duration and maintenance therapy should also be investigated.

It is not entirely clear whether responses to decitabine in vivo are related to hypomethylation or cytotoxicity. The observation of decreasing responses with increasing dose favors hypomethylation, but this question is far from being definitively answered. Moreover, even if hypomethylation is the mechanism mediating responses, events downstream remain to be defined. Possibilities include:

- Direct cell death signaling by hypomethylation, perhaps through reactivation of retrotransposons
- Induction of differentiation
- Induction of senescence
- Induction of apoptosis through reactivation of proapoptotic molecules [45]
• Induction of immune responses through modulation of tumor antigens [46] or the host’s immune system

As mentioned earlier, loss of methylation of the p15 tumor-suppressor gene after multiple cycles was observed in patients with MDS responding to decitabine, but p15 hypomethylation acutely after cycle 1 did not correlate with response in separate studies. Multiple cycles may be needed to achieve enough tumor-suppressor gene hypomethylation – a molecular property that may explain the clinical patterns of response. Overall, the molecular mediators of decitabine effect (beyond hypomethylation) remain to be clarified.

A key issue in the management of MDS is to reduce its heterogeneity using molecular profiles, which will then be essential to select patients for therapy. The IPSS uses a combination of clinical data with cytogenetics to achieve a certain degree of selection [47], but it remains imperfect. More importantly, the IPSS does not predict who is going to respond to decitabine or other treatment modalities in MDS. A concerted effort to supplement the IPSS using gene-expression profiles is essential to making progress in this disease.

In moving forward, it is important to consider the relative benefits and properties of the two hypomethylating agents – azacitidine and decitabine. While both agents inhibit methylation, they are not identical or interchangeable. Azacitidine incorporates into RNA and inhibits RNA translation [15]. The contribution of this property to clinical efficacy may be important but has not been studied. Only after inefficient conversion to decitabine does azacitidine become a hypomethylating agent. Clinically, comparing the Phase III studies of azacitidine and decitabine the response rates are similar, although the population of patients treated with decitabine was more advanced (higher IPSS score, longer time from treatment). Of note, responses seem to occur earlier with decitabine than azacitidine. Noncomparative Phase II studies suggest a higher CR rate with decitabine, though this observation may have related to persistent efforts at optimizing decitabine schedules, effects that are still to be done for azacitidine. Overall, direct comparative studies of the two drugs are needed, but the distinction of their mechanisms of action indicate that there is a likely role for both drugs in MDS.

The future use of decitabine will likely be in combination with other agents. This could be thought of in two types of combinations:

• Combinations that augment its epigenetic effect
• Combinations that take advantage of its epigenetic effects.

Combinations of decitabine and histone deacetylase inhibitors (HDACi) are synergistic in reactivating gene expression [23], and combinations with inhibitors of methylated-DNA binding proteins or histone H3 lysine 9 methyltransferases are also attractive possibilities. Based on in vitro synergistic activity, trials combining decitabine with the HDACi’s valproic acid, depsipeptide and suberoylanilide hydroxamic acid are ongoing. Separately, decitabine has been shown in vitro to sensitize cells to the effects of biologic therapy such as retinoic acid [48] and to increase the expression of pro-apoptotic molecules [45], which may enhance the efficacy of classic chemotherapeutic agents. It has also been demonstrated to reverse drug resistance in selected cases [49]. Clinical trials investigating such combination therapies are underway.

The next frontier for decitabine is to move beyond MDS. There is no evidence for particular methylation profiles in MDS that would make this disease uniquely sensitive to hypomethylating agents [5]. It may simply be that responses in MDS were made possible by the need to use low doses of the agent in this disease and the possibility of treating patients with multiple cycles. It is imperative to now test this approach (lower doses, multiple cycles) in other malignancies, including solid tumors. In fact, there is substantial evidence for decitabine activity in other hematologic malignancies such as AML [34] and CML [17]. Renewed interest in this agent led to ongoing trials (alone or in combination) in various malignancies, and the results of these should be available within the next few years. As a single agent, these include trials in previously untreated older patients with AML, in imatinib-resistant CML, in relapsed or refractory CLL, as well as solid tumor trials in lung cancer, prostate cancer, melanoma, lymphoma and others. Combinations involving decitabine and either classical chemotherapeutics or HDACi are also being tested in AML, ALL, CML and various solid tumors such as refractory ovarian cancer and breast cancer.

Conclusion
Hypomethylating agents reverse gene silencing, which appears critical to maintaining the neoplastic phenotype. Decitabine shows significant
promising in MDS in clinical trials, and its use will become widespread, at least for myeloid malignancies. Although many questions regarding this agent remain to be answered, including dose and in vivo mechanisms of action, clinical benefits are already apparent, and more impressive benefits will come from a combination of therapeutic approaches. In the long run, it is hoped that such therapy will contribute to achieving actual cures of human malignancies.

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<tr>
<td>DNA methylation is an epigenetic modification responsible for silencing of gene transcription.</td>
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<tr>
<td>Inappropriate inhibition of the transcription of certain genes, such as tumor-suppressor genes and genes involved in DNA repair, can lead to unregulated growth and proliferation of cells in both solid tumors and hematologic malignancies.</td>
</tr>
<tr>
<td>Decitabine (5-aza-2'-deoxycytidine) is a potent and specific inhibitor of DNA methyltransferase and is a hypomethylating agent. It has dual effects on neoplastic cells, including reactivation of silenced genes and differentiation at low doses, and cytotoxicity at high doses.</td>
</tr>
<tr>
<td>Decitabine at low doses is an effective treatment in advanced MDS, with manageable toxicity (primarily myelosuppression).</td>
</tr>
<tr>
<td>Decitabine in vivo mechanisms of action, optimal dosing, relative efficacy compared to azacitine (5-aza-dC) and efficacy in other malignancies (including solid tumors) remain to be clarified</td>
</tr>
<tr>
<td>Clinical trials exploiting combination epigenetic therapy or making use of gene reactivation are currently ongoing.</td>
</tr>
</tbody>
</table>

**Bibliography**


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