Therapies with Diverse Mechanisms of Action Kill Cells by a Similar Exponential Process in Advanced Cancers

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Abstract

Successful cancer treatments are generally defined as those that decrease tumor quantity. In many cases, this decrease occurs exponentially, with deviations from a strict exponential being attributed to a growing fraction of drug-resistant cells. Deviations from an exponential decrease in tumor quantity can also be expected if drugs have a nonuniform spatial distribution inside the tumor, for example, because of interstitial pressure inside the tumor. Here, we examine theoretically different models of cell killing and analyze data from clinical trials based on these models. We show that the best description of clinical outcomes is by first-order kinetics with exponential decrease of tumor quantity. We analyzed the total tumor quantity in a diverse group of clinical trials with various cancers during the administration of different classes of anticancer agents and in all cases observed that the models that best fit the data describe the decrease of the sensitive tumor fraction exponentially. The exponential decrease suggests that all drug-sensitive cancer cells have a single rate-limiting step on the path to cell death. If there are intermediate steps in the path to cell death, they are not rate limiting in the observational time scale utilized in clinical trials—tumor restaging at 6- to 8-week intervals. On shorter time scales, there might be intermediate steps, but the rate-limiting step is the same. Our analysis, thus, points to a common pathway to cell death for cancer cells in patients.

See all articles in this Cancer Research section, "Physics in Cancer Research."

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Introduction

In a landmark paper published in Cancer Research in 1964 that described a mouse leukemia model, Skipper formulated two laws of tumor kinetics that have been influential in designing treatment schedules and combination therapies (1, 2). The first law states that dividing cancer cells if left undisturbed grow exponentially. The second law states that when treated with a fixed amount of a therapy, the fraction of cancer cells killed remains the same irrespective of the total number of cancer cells. Although the cellular mechanism of the first law can be traced to symmetric cancer cell division, the molecular roots of the second law are still unknown. For example, as a tumor becomes smaller one could expect a larger fraction might be killed if a fixed amount of a therapy is being used, or if the drug is not uniformly distributed in a tumor, one may anticipate that some parts of the tumor will be more susceptible than others. The second law might also be in conflict with the fact that tumors are heterogeneous. Recent evidence highlighting the genetic diversity of tumors (3) suggests that the cells comprising a tumor have different susceptibilities to killing by a given therapy. Therefore, one might argue a less susceptible fraction is left behind, and the fraction of cells killed with the same dose should decrease with each consecutive drug administration. In agreement with Skipper (Fig. 1), we have previously shown through analysis of tumor measurements obtained from patients that tumor growth occurs exponentially and that the rate of this exponential growth is constant (4–8). The rates are far slower than those of the leukemia models used by Skipper, but the exponential nature of growth was confirmed. We have further shown that in patients with advanced metastatic cancer, the growth rate constant correlates well with overall survival. Although these data have additionally suggested that the regression of tumors is also exponential, we wished to examine other possibilities for the regression of tumor, given the existence of numerous proposed models of how therapies affect tumors. To do this, we mathematically modeled the occurrence of cancer cell death in several ways and analyzed tumor measurements or biomarker data from clinical trials in which a diverse group of anticancer agents was studied in advanced cancers. In analyzing data from these trials, we will show that although the therapies are mechanistically different, ranging, for example, from microtubule-targeting agents to activated T cells, in all...
Figure 1. From ref. 1, “Chart 4”—hypothetical illustration of the possible importance of drug level and schedule in attempts to achieve “cell cure” in early experimental leukemia (L1210) animals. A, untreated controls; number of leukemic cells quadruples daily until the number reaches about 10^9, at which time the animals die. B, daily drug treatment; low level, long term (until death); plotted to represent a daily 50 per cent “drug kill” of the animals’ leukemic cell population and a daily quadrupling of the surviving leukemic cells. Increase in host life span was achieved, but “cell cure” was not approached. C, daily drug treatment; moderate level, long term; plotted to represent a daily 75% “drug kill” of the animals’ leukemic cell population; in finite host survival if cumulative drug toxicity, development of drug resistance within the leukemic cell population or the blood-brain barrier problem did not intervene. D, daily drug treatment; high level, short term; plotted to represent a daily 99% “drug kill” of the animals’ leukemic cell population, no other complications, and “cure” of a 10^5 cell inoculum. In our actual experience, a single maximum dose has been most effective with this very rapidly proliferating experimental disease. Adapted from Skipper (1).
cases, the sensitive tumor cells disappear exponentially. We propose, based on general mathematical grounds, that there is a common feature by which cells die when treated with anticancer agents.

Results

We present three theoretical models: (i) a “constant fraction or exponential model,” where a constant fraction of cells is killed with each drug administration; (ii) a “constant number model,” where a constant number of cells are killed with each treatment; and (iii) a “tumor surface model,” where only (principally) cells on the surface of the tumor are killed with each treatment (Fig. 2). All three models can be analyzed using a simple mathematical approach.

To obtain a relation between the number of sensitive cells and time, we can express at some point of time the relation between the number of sensitive cells at that time and at a time shortly before that time. If the number of cancer cells in the tumor is \( N \) then

\[
N(\text{at time } t + \Delta t) = N(\text{at time } t) - N_{\text{killed}}(\text{between time } t \text{ and } t + \Delta t),
\]

where \( N_{\text{killed}} \) is the number of cells killed by a therapy during time interval \( \Delta t \). For the three models then, we have the following:

- Constant fraction or exponential model: \( N_{\text{killed}} \) in any time interval \( \Delta t \) during treatment is \( \Delta t \cdot f \cdot N \), where \( f \) is a fraction of the total number of cells \( (N) \) in the tumor at time \( t \). The fraction \( f \cdot N \) is the number of cells killed per unit time and is proportional to the total number of cells in the tumor.
- Constant number model: \( N_{\text{killed}} \) in any time interval \( \Delta t \) during treatment is \( \Delta t \cdot C \), where \( C \) is the number of cells killed per unit time. \( N_{\text{killed}} \) in time interval \( \Delta t \) is constant and is “independent of the number of cells in the tumor,” being dependent only on the time interval \( \Delta t \).
- Tumor surface model: \( N_{\text{killed}} \) is the number of cells on the surface of the tumor and if we assume that the tumor is spherical we can obtain an expression for the relation between the fraction of cells on the surface of the tumor and the total number of cells in the tumor (see the Supplementary Information).

One can cast the three models in a differential form by using \( \Delta N \) to mean the change in cell number during time \( \Delta t \), with \( N \) as the total number of cells at the outset. The equations describing the three models are:

- Constant fraction or exponential model, where the same fraction of cells is killed with each treatment and the number is that fraction:
In the constant fraction or exponential model, the (sum of)
the number on the right-hand side contains only a number.
In the tumor surface model, the volume decreases as the
cubic root of time. Given the above theoretical models,
we examined data from a diverse group of clinical trials to investigate how different
therapies affect tumors—specifically how these different ther-
pies bring about regression of tumors. In most patients, the
tumor first shrinks at the start of treatment and after reaching
a minimum, increases in size, as drug resistant cells comprise
an increasingly larger fraction of the tumor. We have shown
and reported previously that growth of the resistant fraction is
well modeled as an exponential, which we have estimated with
the growth rate constant, \( g \) (4–8). Whether the resistant
fraction preexists before therapy begins, or resistance is
acquired after therapy has begun, there will be a time when
the sensitive cells are continuing to be killed while the resistant
cells are growing. The exponentially growing fraction of cells
also exists during that part of the time course, corresponding to
a decrease in the overall tumor size—a decrease that is
occurring because the quantity of tumor being killed is still
greater than the quantity growing exponentially, so the net
result is the reduction in size. Because these two processes are
occurring concurrently, we include in our analysis of the killing
process, the exponentially growing fraction in each model as
defined below. The equations that describe the tumor vol-
ume (number of cells) and the longest diameter of the tumor
are shown in Table 1.

The constants \( \phi, d, \) and \( g \) are estimated from the data of
quantities of tumor obtained while a patient receives a given
therapy. The data are either measurements of the longest
diameter of tumor masses seen radiographically or the values
of serum markers recorded as treatment is administered and
response is assessed. Note that the exponential model is
described by the same equation whether volume or diameter
is used. The fraction or proportion of the initial tumor that is
sensitive to treatment and will eventually decay or regress is
represented by \( \phi \) and is to be distinguished from the fraction
that is killed with each cycle of treatment. The decay or
regression rate constant represented by \( d \) describes the rate at
which the fraction of tumor that is sensitive to the therapy is
disappearing. The growth rate constant represented by \( g \)
describes the rate at which the fraction of tumor that is
resistant or relatively resistant to the therapy is growing, and
as we have discussed, this growth occurs exponentially.
Finally, the fraction of the initial tumor that is resistant or
relatively resistant to the therapy is equal to \( (1 - \phi) \), given
that \( \phi \) has been defined as the fraction of the initial tumor
that is sensitive to the therapy. All the analyses of the killing
process include the exponentially growing fraction \( (1 - \phi) \cdot 
\exp(\phi t) \), where \( (1 - \phi) \) is the fraction of the tumor resistant or
relatively resistant to the therapy in each model. Although the
constant fraction or exponential model represents the expo-
ential decrease we have reported before (4–8), the other two
models—constant number and tumor surface—represent
nonexponential models.

\[
\frac{\Delta N}{\Delta t} = -\text{number} \cdot N
\]  
\[ (2) \]

- In the constant number model, where the same number of cells are
  killed with each treatment:
  \[
  \frac{\Delta N}{\Delta t} = -\text{number}
  \]  
\[ (3) \]

- In the tumor surface model, where only (principally) cells on the
  surface of the tumor are killed with each treatment:
  \[
  \frac{\Delta N}{\Delta t} = -\text{number} \cdot N^{2/3}.
  \]  
\[ (4) \]

In each of the three cases, the number on the right-hand side
differs depending on the details of the model. However,
the details do not alter the fact that:

- In the constant fraction or exponential model, this number,
  representing the fraction of tumor killed, multiplies the first
  power of the total cell number \( N \) in the tumor.
- In the constant number model, the right-hand side contains
  only a number.
- In the tumor surface model, the number multiplies the two-
 third power of the total number of cells \( N \) in the tumor.

We have assumed that the rate at which a therapy kills
cells does not vary with time. This might not be the case. For
example, combination therapies with antiangiogenic drugs
that possibly normalize the vasculature should be expected
to lead to changes in the rate of killing. Reducing angiogen-
esis could starve the tumor of nutrients and also have a
negative effect on the delivery of a therapy, thus slowing the
kill rate, or normalization of leaky blood vessels with a
decrease in their tortuosity could improve blood flow so that
delivery of a therapy to the tumor improves, increasing
kill rate.

The number of cells in a tumor correlates with its volume.
Given this, the solutions of the equations describing the three
models are displayed in Fig. 3A:

- In the constant fraction or exponential model, the volume
decreases exponentially with time.
- In the constant number model, the volume decreases linearily
  with time.
- In the tumor surface model, the volume decreases as the
  third power.

Often the sum of the longest measured linear distances or
the longest diameters of the radiographically assessed tumor
are used as a criterion for response as described in RECIST. In
this case, the solutions of the equations describing the three
models are displayed in Fig. 3B:

- In the constant fraction or exponential model, the (sum of
  the) longest diameter still decreases exponentially but with
  one third of the rate.
The analysis of clinical data is summarized in Table 2 (9–17). The measurements in the case of prostate cancer and multiple myeloma are "volumetric," because serum PSA (in patients with prostate cancer) and M protein levels (in patients with multiple myeloma) were used as the measures of tumor quantity. The rest of the trials used RECIST guidelines to assess efficacy, so that the sums of the longest linear diameters of the tumor masses assessed radiographically were the

Figure 3. A, graphs depicting the solutions of formulas (for constant fraction or exponential model, constant number model, and tumor surface model), where tumor volume (or number of cells) is assessed. B, graphs depicting the solutions of the same formulas as in A, where the longest linear distance or longest diameter of the tumor is assessed.
Table 1. Equations describing the tumor volume and the longest diameter of the tumor

<table>
<thead>
<tr>
<th>Model</th>
<th>Exponential regression model</th>
<th>Nonexponential (Ne) regression models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells killed</td>
<td>Constant fraction</td>
<td>Constant number</td>
</tr>
<tr>
<td>Volume =</td>
<td>$\phi \cdot e^{-dt} + (1 - \phi) \cdot e^{gt}$</td>
<td>$\phi \cdot d \cdot t + (1 - \phi) \cdot e^{gt}$</td>
</tr>
<tr>
<td>Diameter =</td>
<td>$\phi \cdot e^{-dt} + (1 - \phi) \cdot e^{gt}$</td>
<td>$\phi \cdot d \cdot t + (1 - \phi) \cdot e^{gt}$</td>
</tr>
</tbody>
</table>

The data analyzed here, showing tumor regression in most cases occurs exponentially, argues against the existence of an intermediate step in the process of cell death. This does not mean cells that are damaged cannot repair their damage and rejoin the viable fraction. This is shown in Fig. 5, where each treatment damages some cells, a fraction of which die while the remaining repair the damage and rejoin the viable fraction. In the latter case, if the fraction that repairs the damage is constant, then cell death occurs exponentially. It also does not mean only one molecular event occurs before cell death. A complex set of events might take place, but these must always lead to cells that are either fully viable or dead, that is, the ensuing treatment begins from the same initial state as the previous treatment administration. That there is no intermediate step may be a consequence of the doses used with cancer therapies; if these doses are always administered at high enough amounts, then the different steps required for cell death are accomplished within one treatment. This seems unlikely given the observation of exponential cell death with a myriad of drugs and with modalities other than drugs. But if the reason an intermediate step is not "detected" is because doses are excessive, then a deviation from exponential or fractional cell death would be an indication the treatment is insufficient in quantity.
Table 2. Tabulation of which equation best fit individual clinical datasets

<table>
<thead>
<tr>
<th>Cancer histology</th>
<th>Therapy</th>
<th>N</th>
<th>dx</th>
<th>gx</th>
<th>gd</th>
<th>g + d + μ</th>
<th>Percent of total</th>
<th>Of regression</th>
<th>Nonexponential models</th>
<th>Percent of total</th>
<th>Of regression</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatea</td>
<td>Thalidomide + Taxotere (9)</td>
<td>55</td>
<td>5</td>
<td>12</td>
<td>17</td>
<td>15</td>
<td>89.1%</td>
<td>86%</td>
<td>Ne1</td>
<td>Ne2</td>
<td>Ne3</td>
<td>Ne4</td>
</tr>
<tr>
<td>RCCb</td>
<td>Bevacizumab (10)</td>
<td>34</td>
<td>1</td>
<td>3</td>
<td>18</td>
<td>9</td>
<td>91.2%</td>
<td>90.3%</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Prostatea</td>
<td>ATTP/ARTP (11)</td>
<td>98</td>
<td>8</td>
<td>13</td>
<td>27</td>
<td>44</td>
<td>93.9%</td>
<td>92.9%</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Breastb</td>
<td>Capecitabine + Ixabiprole (12)</td>
<td>211</td>
<td>40</td>
<td>5</td>
<td>100</td>
<td>37</td>
<td>86.3%</td>
<td>85.9%</td>
<td></td>
<td>11</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Breastb</td>
<td>Capecitabine (12)</td>
<td>160</td>
<td>33</td>
<td>17</td>
<td>64</td>
<td>16</td>
<td>81.3%</td>
<td>79%</td>
<td></td>
<td>2</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>MMF</td>
<td>Bortezomib ± Doxil (13)</td>
<td>259</td>
<td>57</td>
<td>17</td>
<td>75</td>
<td>81</td>
<td>88.8%</td>
<td>88%</td>
<td></td>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MMF</td>
<td>Bortezomib (13)</td>
<td>283</td>
<td>49</td>
<td>14</td>
<td>92</td>
<td>89</td>
<td>91.3%</td>
<td>90.8%</td>
<td></td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostatea</td>
<td>Ketoconazole + Aclidronate (9)</td>
<td>67</td>
<td>5</td>
<td>17</td>
<td>23</td>
<td>18</td>
<td>94%</td>
<td>92%</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>RCCb</td>
<td>Interferon (15, 16)</td>
<td>210</td>
<td>48</td>
<td>37</td>
<td>71</td>
<td>20</td>
<td>83.8%</td>
<td>79.2%</td>
<td></td>
<td>6</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>RCCb</td>
<td>Sunitinib (15, 16)</td>
<td>300</td>
<td>56</td>
<td>8</td>
<td>153</td>
<td>60</td>
<td>92.3%</td>
<td>92.1%</td>
<td></td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Prostatea</td>
<td>Vaccine</td>
<td>67</td>
<td>1</td>
<td>45</td>
<td>8</td>
<td>1</td>
<td>82.1%</td>
<td>45%</td>
<td></td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>RCCb</td>
<td>T-cell-based immunotherapy</td>
<td>62</td>
<td>8</td>
<td>6</td>
<td>26</td>
<td>11</td>
<td>82.3%</td>
<td>80.4%</td>
<td></td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RCCb</td>
<td>T-cell-based immunotherapy</td>
<td>51</td>
<td>7</td>
<td>2</td>
<td>23</td>
<td>10</td>
<td>82.4%</td>
<td>81.6%</td>
<td></td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MTCb</td>
<td>Vandetanib (17)</td>
<td>188</td>
<td>45</td>
<td>7</td>
<td>98</td>
<td>16</td>
<td>88.3%</td>
<td>87.8%</td>
<td></td>
<td>2</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>All</td>
<td>Various</td>
<td>2,027</td>
<td>361</td>
<td>203</td>
<td>795</td>
<td>427</td>
<td>88.1%</td>
<td>86.8%</td>
<td></td>
<td>48</td>
<td>18</td>
<td>37</td>
</tr>
</tbody>
</table>

NOTE: Each patient dataset appears only once under the best-fit model (formula) for that particular data. Datasets with four or more points were used in the analysis. The eight models were fit for each dataset. P-value for the fit had to be <0.1. To select the best model for those with more than one valid fit, the AIC was calculated for each model, AIC = 2k – 2lnL, where k is the number of parameters and lnL is the log likelihood; the preferred model was selected as the one that minimizes the AIC.

Cancer histology, assessment methods: *Serum PSA; †Radiographic imaging, CT or MRI; ‡M-spike, immunoglobulin levels.

Formulas: See text for details. [dx, data show only regression and no evidence of growth; gx, data show only growth and no evidence of regression].

\[
dx: f(t) = \exp(-d \cdot t) - 1; \quad gx: f(t) = \exp(g \cdot t) - 1; \quad gd: f(t) = \exp(-d \cdot t) + \exp(g \cdot t) - 1; \quad g + d + \mu \cdot f(t) = \mu \cdot \exp(-d \cdot t) + (1 - \mu) \cdot \exp(g \cdot t),
\]

\[
Ne1 = (\mu - d \cdot t) + (1 - \mu) \cdot e^t; \quad Ne2 = (\mu - d \cdot t) + (1 - \mu \cdot s) \cdot e^t; \quad Ne3 = (\mu - d \cdot t) + (1 - \mu \cdot s) \cdot e^t; \quad Ne4 = (\mu - d \cdot t) + (1 - \mu \cdot s) \cdot e^t.
\]

The percentage of calculations: \( N = (dx) + (gx) + (gd) + (g + d + \mu) + (Ne1) + (Ne2) + (Ne3) + (Ne4).

The percentage of total (exponential regression models) = (dx) + (g + d + \mu) + (gd) + (Ne1) + (Ne2) + (Ne3) + (Ne4)/N.

The percentage of decay (exponential regression models) = (dx) + (g + d + \mu) + (gd) + (Ne1) + (Ne2) + (Ne3) + (Ne4) - (gx).

The percentage of decay (nonexponential regression models) = (Ne1) + (Ne2) + (Ne3) + (Ne4) - (gx).

Abbreviations: Ne, nonexponential; none, data did not fit any model; \( \mu \), fraction of that sensitive to the therapy being administered; RCC, renal cell carcinoma; MM, multiple myeloma; MTC, medullary thyroid carcinoma; ATTP, Avastin (bevacizumab) + Thalidomide + Taxotere + Prednisone; ARTP, Avastin (bevacizumab) + Revlimid (lenalidomide) + Taxotere + Prednisone; Doxil, liposomal doxorubicin.
Our data also imply that although a tumor may be composed of cells harboring different mutations and expressing crucial genes at different levels, the cells in tumor die through a common pathway. This conclusion is reached, because if different pathways existed and the rates of cell death for each of pathways were different, the decrease of the tumor quantity would be nonexponential. This does not mean cells in all tumors must die in the same way. Cells in a lymphoma or a testicular cancer may die as a result of apoptosis, whereas cells in another solid tumor die via a different pathway. Alternately all cancer cells in all tumors could die via apoptosis, only at varying rates. In this scenario, the rate-limiting step could be cytochrome C release or caspase activation. Thus, the original observations of Skipper on the L1210 leukemia model suggesting meaningful increases in survival depended on increasing the fraction of tumor cells that die following treatment is more relevant for solid tumors than we have considered in recent years. If we
kill the same fraction of tumor cells at each step, the data imply that we must increase that fraction—a very old concept, but one now supported by actual patient data.

In summary, we have discussed several models of cell death following treatment of human cancers. We have analyzed data from a diverse group of clinical trials and demonstrate that in patients treated with diverse therapies, cell death occurs preferentially in an exponential manner. A corollary of this exponential cell death is that there can be no intermediate with a significantly different rate-limiting step in the occurrence of cell death; cells are not incrementally damaged by successive therapies but rather, having been damaged by a therapy, either die or repair the damage. A second corollary is that cell death in a tumor follows a common pathway. Together with previous analyses demonstrating exponential growth as the preferred pattern of tumor growth, we hope this information can be used to better understand how therapies work and how to make them better.

Figure 5. Three scenarios of treatment action. In the scenario shown in the top, a treatment affects a constant fraction of 30% of cells (red) and these die. In the scenario depicted in the middle, some of the treatment-affected cells (green) repair their damage, rejoin the viable tumor cell pool, and continue contributing to the growth of the tumor, reducing the fraction of cells killed to 20%. Here, drug-resistant cells that increase cell number irrespective of treatment are not shown. Also the sensitive cells (blue) are assumed not to be dividing between treatments. Data obtained at the next assessment cannot distinguish between these two possibilities and only captures the net regression rate. In the bottom, a scenario in which a constant (18) number of cells are killed each time the treatment is administered. With the first treatment, the same number of cells was killed, but subsequently the cells were killed at increasingly larger proportions in the bottom scenario, because the number of cells that were killed stayed the same, whereas in the top and middle scenarios, the number of cells killed decreased in time.
Disclosure of Potential Conflicts of Interest

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Disclaimer

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Authors’ Contributions

Conception and design: K.B. Blagoev, A.T. Fojo Development of methodology: K.B. Blagoev, W.D. Stein, A.T. Fojo Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Yang, A.T. Fojo Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.B. Blagoev, J. Wilkerson, S.E. Bates, A.T. Fojo

References

Exponential Process in Advanced Cancers
Therapies with Diverse Mechanisms of Action Kill Cells by a Similar


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