I. Carcinogenesis

Well-known news anchor, Peter Jennings, died of small cell lung cancer this year. He was a cigarette smoker most of his life.

1. Describe two different epidemiological (population) studies that implicate cigarette smoking as a major risk factor for lung cancer.

1. A parallel rise in cigarette smoking and lung cancer incidence in both males and females, offset by 20-30 years.

2. Populations where cigarette smoking is rare, such as with Mormons, show a very low incidence of lung cancer.

3. A linear correlation between the number of cigarettes smoked per day and lung cancer incidence.

2. Some observations in sequential cellular changes that occur in small cell lung cancer (SCLC) are losses at chromosomal locations 3p and 6p of genes encoding for a transcription factor and a tumor suppressor protein (p16\textsuperscript{INK}). Dysplasia follows and appears to involve p53 mutations and loss of the mismatch repair gene hMSH3. Mutations of k-ras and cyclin D, protooncogenes, as well as in a p73 tumor suppressor gene are associated with tumor invasion.

Based on your knowledge of the carcinogenic process, what would you tell someone who asked you why some non-smokers, like Christopher Reeve's wife (Dana 44 y.o.) can be stricken with SCLC while some smokers do not get lung cancer? Make specific reference to each of the factors mentioned above in describing the three stages of the carcinogenic process.

Carcinogenesis is a multifactorial, multistage process that usually requires several genetic and epigenetic changes in cells. Initiation can occur via mutations in DNA caused by chemicals, viruses, inherited defects (3p and 6p genes and loss of the tumor suppressor protein p16\textsuperscript{INK}). The promotional process occurs by which the initiated cell has been changed to a mutated phenotype (p53 mutations and loss of the mismatch repair gene hMSH3). Mutations in tumor suppressor genes, such as k-ras and cyclin D, could lead to loss of cell adhesion, and tumor invasion in progression of the tumor to a malignant stage.

As stated above, carcinogenesis if a multifactorial, multistage process that usually requires several genetic and epigenetic changes in cells. Some may not be stricken with SCLC because they do not have the inherited defects that can allow for initiation. Others, like Dana, may have a genetic predisposition to SCLC (like losses at chromosomal locations 3p and 6p) and initiation is triggered by environmental effects, in this case, second hand smoke.
II. Alkylation is implicated in many carcinogenic reactions and is the underlying principle behind many anticancer agents. Show how the following compounds could alkylate DNA (arrow pushing). Phase I or Phase II metabolism may be required to generate the reactive species.

1. Bulsulfan

\[
\begin{align*}
\text{H}_2\text{C} & \xrightarrow{\text{Nu-DNA-Nu}} \text{SO} \xrightarrow{\text{Nu}} \text{O} \\
\text{H}_3\text{C} & \xrightarrow{\text{Nu}} \text{SO} \xrightarrow{\text{Nu}} \text{Cl} \\
\text{Nu-DNA-Nu} & \xrightarrow{\text{Nu}} \text{O} \\
\end{align*}
\]

2. Vinyl chloride

\[
\begin{align*}
\text{H} & \xrightarrow{\text{Nu-DNA-Nu}} \text{C} \xrightarrow{\text{Nu}} \text{CH}_2 \\
\text{Cl} & \xrightarrow{\text{Nu-DNA-Nu}} \text{CH}_2 \\
\text{Nu-DNA} & \xrightarrow{\text{Nu-DNA}} \text{O} \\
\end{align*}
\]

3. N-nitroso nicotine

\[
\begin{align*}
\text{H} & \xrightarrow{\text{Nu-DNA-Nu}} \text{P}_4\text{SO} \xrightarrow{\text{Nu}} \text{O} \\
\text{N} & \xrightarrow{\text{Nu-DNA-Nu}} \text{H} \\
\text{OH} & \xrightarrow{\text{Nu-DNA-Nu}} \text{O} \\
\end{align*}
\]

4. 3-methylcholanthrene (3-MC)

\[
\begin{align*}
\text{Bay region: sterically hinders attack by epoxide hydrolase.} \\
\text{H}_3\text{C} & \xrightarrow{\text{P}_4\text{SO}[\text{O}]} \text{P}_4\text{SO} \xrightarrow{\text{Water}} \text{OH} \\
\text{Nu} & \xrightarrow{\text{Nu-DNA-Nu}} \text{OH} \\
\end{align*}
\]
III. Neuroblastoma is a cancer of embryonic nerve cells usually in the peritoneal region and often associated with adrenal glands. It occurs most commonly in young children. One regimen (CODO) consists of Cyclophosphamide (Cytoxan), Oncovin (Vincristine), Dacarbazine (DTIC), and Doxorubicin (Adriamycin). Use the table below to describe each agent with regards to therapeutic class, chemical subclass, cell cycle selectivity, major toxicity and mechanisms of action.

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Cyclophosphamide</th>
<th>Oncovin</th>
<th>Dacarbazine</th>
<th>Doxorubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating (DNA damaging) agent</td>
<td>Antimitotic</td>
<td>Alkylating (DNA damaging) agent</td>
<td>Topoisomerase II inhibitor</td>
<td></td>
</tr>
<tr>
<td>Chemical Subclass</td>
<td>Nitrogen mustard</td>
<td>Vinca alkaloid</td>
<td>Triazene</td>
<td>Anthracycline antibiotic</td>
</tr>
<tr>
<td>Cell Cycle</td>
<td>CCNS</td>
<td>CCS for M-phase</td>
<td>CCNS</td>
<td>CCNS</td>
</tr>
<tr>
<td>Major Toxicity</td>
<td>BMD</td>
<td>Peripheral neuropathy</td>
<td>BMD</td>
<td>BMD, peripheral neuropathy, cardiotoxicity</td>
</tr>
<tr>
<td>Mechanisms of Action</td>
<td>A prodrug that is metabolized to a phosphoramidemustard that crosslinks DNA via formation of aziridinium ions.</td>
<td>Binds to tubulin dimers and leads to blockage of polymerization of microtubules. This leads to blockage of mitosis at the metaphase.</td>
<td>A prodrug that is oxidatively demethylated to form a triazene that methylates DNA.</td>
<td>Binds to polymeric tubulin which leads to stabilization of microtubules so they will not depolymerize. This leads to disruption of mitosis and inhibits BCL2 proteins, therefore, allowing apoptosis.</td>
</tr>
</tbody>
</table>

Based on your answers above, is this a good regimen? Why or why not?

In terms of the phases of the cell cycle targeted, this treatment is effective since all phases of the cell cycle are covered, though not selectively, except for the M-phase. Three drugs overlap on the major toxicities, and therefore, the combination would cause severe BMD for people using it. Perhaps one or more agents should be replaced to reduce the potential for BMD and special toxicities associated with them. Thus, based on toxicity profile, this is probably not a very good regimen.
IV. Ifex-Mesna is sometimes used in place of Cyclophosphomide. Shown below is a partial scheme for the conversion of the prodrug Ifospharmide (A), to its active nitrogen mustard alkylating agent.

a. Show (arrow convention) how B is converted to C.

b. Show the structure of E.

c. Show (arrow convention) how E forms F.

d. Show (arrow convention) how F reacts with DNA and give the structure of the alkylated product G.

e. Briefly explain how G reacts to further damage DNA.

G can form an aziridinium ion which can alkylate DNA by the same mechanism as in part (d). It can also crosslink DNA as shown in product G. (see above)