A French collaborative group chose a different regimen for the combination of IL2 and IFNα as one of the treatments in a three-arm randomised trial (Negrier et al. 1998). They randomised 425 patients to receive: single agent IL2 administered as a 5-day continuous intravenous infusion at a dose of 18 MU/m^2 per day, repeated six times with 3-week intervals (138 patients, group 1); subcutaneous single agent IFNα at a dose of 18 MU three times a week for 23 weeks (147 patients, group 2); or the same IL2 treatment as group 1 but, in addition, IFNα at a dose of 6 MU three times per week during the IL2 cycles (140 patients, group 3). Response rates were 6.5%, 7.5% and 18.6% ($p < 0.001$) for the groups receiving IL2, IFNα and IL2 + IFNα, respectively. At 1 year, the event-free survival was still significantly higher for combination therapy (20%) than for single agent treatment (IL2 15%, IFNα 12%, $p = 0.01$), but there was no significant difference in overall survival among the three groups.

The same collaborative group also addressed the question of cross-resistance between IL2 and IFNα. They showed clearly (Escudier et al. 1999) that, if patients progress on IFNα or IL2 treatment, they are very unlikely to respond to the other cytokine. In fact, even if there was an initial response to first-line IFNα or IL2, a response to second-line therapy with the other cytokine after relapse/progression was very rare: only 4 of 113 patients responded to crossover treatment. Other investigators, however, document different results and have concluded that IL2 subcutaneous therapy alone can be an effective and well tolerated treatment in advanced RCC patients progressed under IFNα therapy (see Lissoni et al. 1992; Bordin et al. 2000).

Biochemotherapy

IL2/IFNα/5FU

RCC is resistant to most chemotherapeutic agents, although vinblastine and 5-fluorouracil (5FU) have some modest activity. The suggestion that cytokine treatment can enhance chemotherapeutic cytotoxicity is supported by early clinical trials. In 1993 Atzpodien and co-workers (1993b) treated 34 patients with advanced RCC with a combination therapy of IL2, IFNα and 5FU. Treatment consisted of 8 weeks of subcutaneous IFNα (6–9 MU/m^2 one to three times weekly) combined sequentially with subcutaneous IL2 (5–20 MU/m^2 three times weekly) for 4 weeks, and then 5FU (750 mg/m^2 intravenous bolus weekly) for 4 weeks. The overall response rate to this regimen was 49%, with 11% of the patients achieving a complete remission.

These encouraging results prompted several phase II studies testing the combination of these three drugs. In 1997 Bukowski summarised seven trials with a total of 262 patients: the overall response rate ranged from 10% to 39% with a mean of 32%, and complete remissions were observed in 0–16% of patients. These trials all had small numbers of patients and differed considerably with regard to the schedules used.

There is one randomised trial (Atzpodien et al. 2001) comparing IL2/IFNα/5FU biochemotherapy to hormonal treatment with tamoxifen. A total of 78 patients with

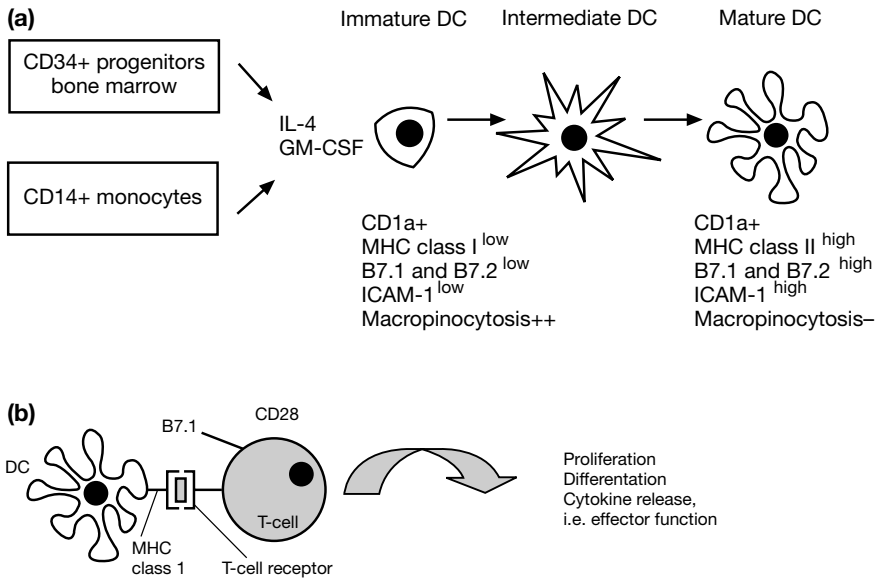

Figure 11.2 (a) Dendritic cells (DCs) may be cultured from CD34+ progenitor cells or CD14+ monocytes using specific cytokines (interleukin-4 [IL4] and granulocyte–macrophage colony-stimulating factor [GM-CSF]). Immature DCs have physiological properties (such as phagocytosis or macropinocytosis) that favour the uptake of tumour or viral antigen. Mature DCs are able to activate T-cell responses more effectively than immature cells, but are less able to take up exogenous antigen. **(b)** Interaction of a DC expressing a tumour antigen on its surface (by an MHC class I molecule) with a CD8+ T cell. In order for the T cell to become activated and release cytokines to recruit further CD8+ T cells, a co-stimulatory interaction between B7.1 and CD28 is mandatory.

ICAM, intercellular adhesion molecule; MHC, major histocompatibility complex.

hypersensitivity reactions) were obtained, in some cases even in late-stage disease. As a result of differences in protocol design, effects of concurrent treatment, DC source, routes of administration, frequency of immunisation and a general lack of accepted (immunological) markers of response, the results of different DC strategies are difficult to compare. A recent study reported anti-tumour reponses from a DC vaccine comprising autologous (self) RCC cells fused with allogeneic (foreign) DCs. This approach has been shown to extremely promising in murine studies, using murine DCs and human breast cancer cell hybrids (Gong et al. 1997). Although some of the experimental details were not substantiated and the study results withdrawn, clear tumour regressions were seen (Kugler et al. 2000). It is possible that clinical improvements may have simply reflected response to autologous tumour similar to that observed in cellular immunisation in other cancers.

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